PCT

WORLD INTELLECTUAL PI
Internatioı

INTERNATIONAL APPLICATION PUBLISHED UNI

WO 9602250A1

(51) International Patent Classification 6 :
A61K 31/445, 31/495

A1

(11

(43) International Publication Date: 1 February 1996 (01.02.96)

(21) International Application Number: PCT/US95/09191

(22) International Filing Date: 20 July 1995 (20.07.95)

(30) Priority Data:
08/277,871 20 July 1994 (20.07.94) US
08/475,990 7 June 1995 (07.06.95) US

(71) Applicants: ACEA PHARMACEUTICALS INC. [US/US]; 213 Technology Drive, Irvine, CA 92718 (US). CoCENSYS, INC. [US/US]; 213 Technology Drive, Irvine, CA 92718 (US).

(72) Inventors: CAI, Sui, Xiong; 3900 Parkview Lane #6B, Irvine, CA 92715 (US). WOODWARD, Richard, M.; 95 Sandcastle, Aliso Viejo, CA 92656 (US). LAN, Nancy, C.; 522 Hermosa Street, South Pasadena, CA 91030 (US). WEBER, Eckard; 1290 Morningside Drive, Laguna Beach, CA 92651 (US).

(74) Agents: ESMOND, Robert, W. et al.; Sterne, Kessler, Goldstein & Fox, Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: HALOPERIDOL ANALOGS AND THE USE THEREOF

(57) Abstract

The invention relates to haloperidol analogs as subtype-selective NMDA receptor ligands and the use thereof for treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Down's syndrome, treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, treating anxiety, convulsions, migraine headaches, glaucoma, chronic pain and inducing anesthesia, as well as for enhancing cognition.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

Haloperidol Analogs and the Use Thereof

Background of the Invention

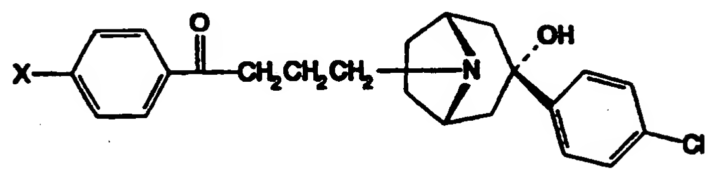
Field of the Invention

The invention is in the field of medicinal chemistry. In particular, the invention relates to haloperidol analogs and the use thereof to treat or prevent neurodegenerative conditions, to induce analgesia, to treat migraine headaches, to treat glaucoma, as anticonvulsants and as cognitive enhancers.

Description of the Prior Art

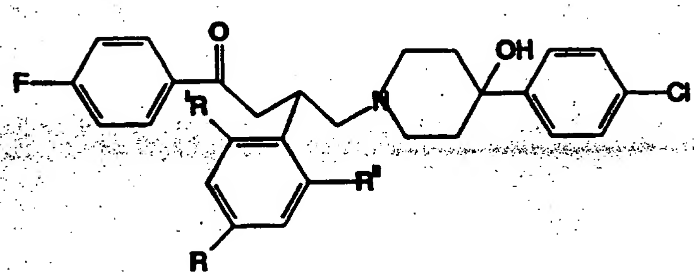
In 1990 a paper appeared in the journal *Synapse* reporting that haloperidol, a therapeutically useful anti-psychotic agent, has neuroprotective effects against N-methyl-D-aspartate (NMDA)-induced brain injury (MacDonald and Johnston, *Synapse 6*:179-188 (1990)). However, the mechanism of action was uncertain. Then, in April 1993 a paper in the *European Journal of Pharmacology* reported that haloperidol is a weak NMDA receptor antagonist (Fletcher and MacDonald, *Eur. J. Pharmacol. 235*:291-295 (1993)). This study used electrical recording techniques to assay NMDA receptors in cultured rat hippocampal pyramidal neurons and concluded that haloperidol is probably a weak partial agonist/competitive antagonist at the strychnine-insensitive glycine binding site. The neuroprotective effects of haloperidol might, therefore, be due to direct inhibition of NMDA receptors.

There are a number of reports directed to the preparation of haloperidol analogs. For example, Langbein, Aldof *et al.* EP 53744, discloses compounds having the Formula:



wherein X = OMe, Me, Br, Cl, F, H.

Sato *et al.* *Chem. Pharm. Bull.* *29*:3134-44 (1981), disclose the following haloperidol analogs, where the inhibitory effects on spontaneous motor activity "were far less than that of haloperidol."



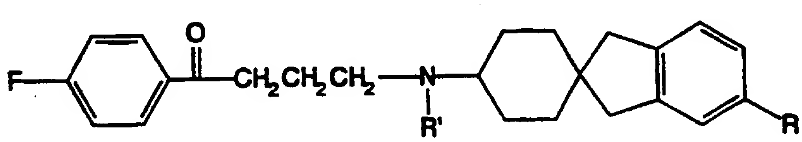
R = R′ = R″ = H

R = R′ = R″ = Me

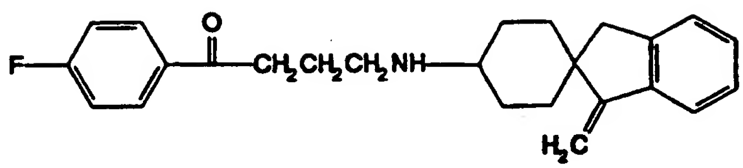
R = OMe, R′ = R″ = Cl.

See also Cascio *et al.*, *Farmaco, Ed. Sci.* *35*:605-14 (1980) and Kitamura *et al.* JP 73-9241.

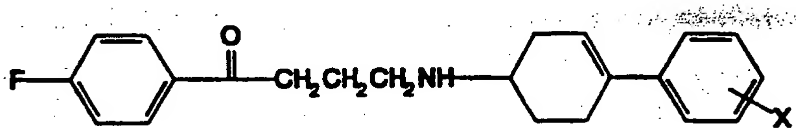
Other examples of haloperidol analogs are taught by Lednicer *et al.*, *J. Org. Chem.* *40*:3839 (1975):



where R = H, OMe, and R′ = H, Me; and

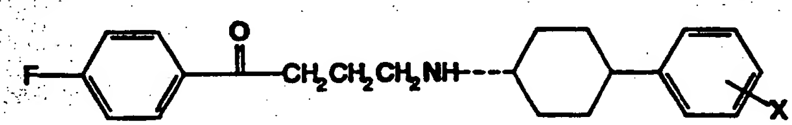


Other examples of haloperidol analogs are taught by Lednicer *et al.*, *J. Med. Chem.* *15*:1235 (1972):



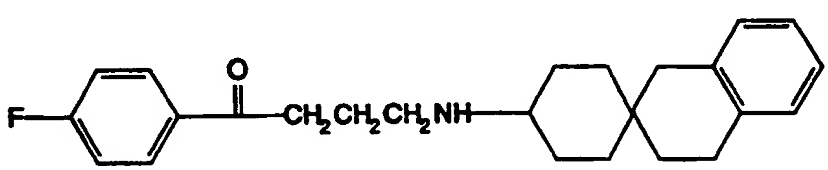
where X = *o*-Me, *m*-Me, *p*-Me, *m*-OMe, *p*-Cl, *p*-F, *o*-CF3, *m*-CF3 and other substituents.

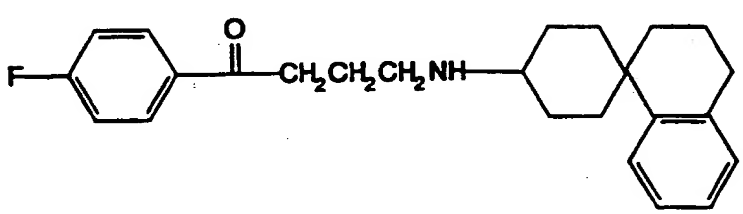
Other examples of haloperidol analogs are taught by Lednicer *et al.*, *J. Med. Chem.* *15*:1239 (1972):



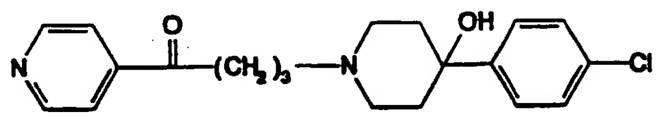
where X = *o*-Me, *m*-Me, *p*-Me, *m*-OMe, *p*-Cl, *p*-F, *m*-CF3 and other substituents.

Another example of haloperidol analogs is taught by Lednicer *et al.*, *J. Org. Chem.* *40*:3844 (1975):



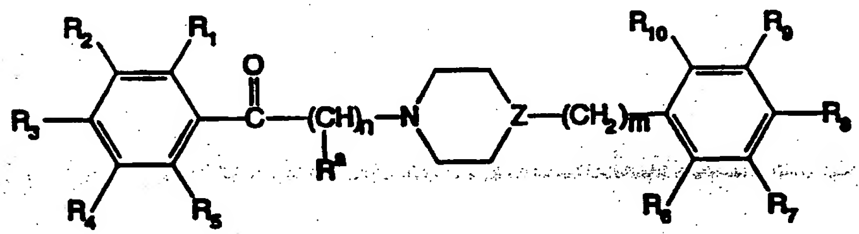


Another example of a haloperidol analog is taught by Makoto Sato *et al.*, *Chem. Pharm. Bull.* *26*:3296 (1978):



Summary of the Invention

The invention relates to a subtype-selective NMDA receptor ligand having the Formula (*I*):



I

wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

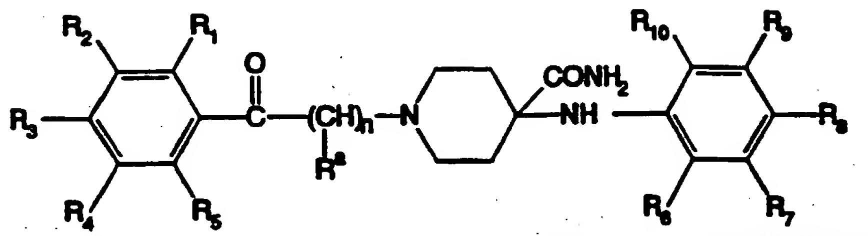
Z is one of N, CH, COH, CCN, CCHO, $CCONH_2$, CCO-alkyl, CCO-alkenyl, CCH_2NHCO-alkyl, CHO-alkyl or CNR^dR^e, wherein R^d and R^e are independently alkyl groups;

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy or carboxy;

n is 1 to 5; and

m is 0 to 3.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*II*):



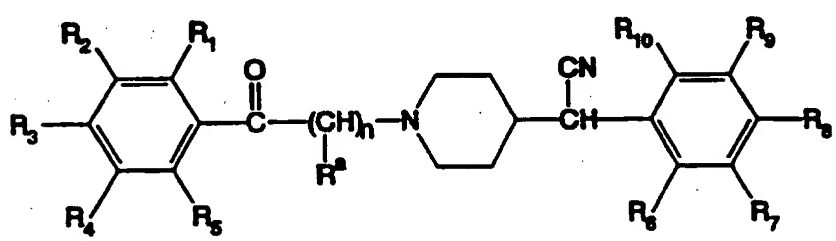
II

wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy or carboxy;

and

n is 1 to 5.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*III*):

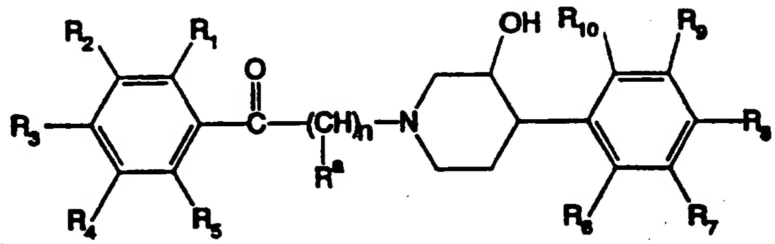


III

wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R^a can vary with each repetitive CH group and is independently hydrogen, alkyl, aryl, hydroxy or carboxy; and

n is 1 to 5.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*IV*):

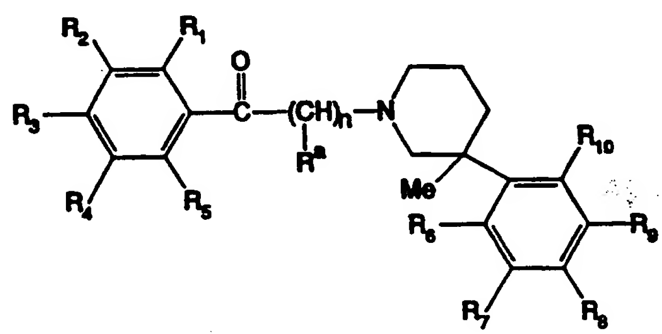


IV

wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R^a can vary with each repetitive CH group and is independently hydrogen, alkyl, aryl, hydroxy or carboxy; and

n is 1 to 5.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*V*):

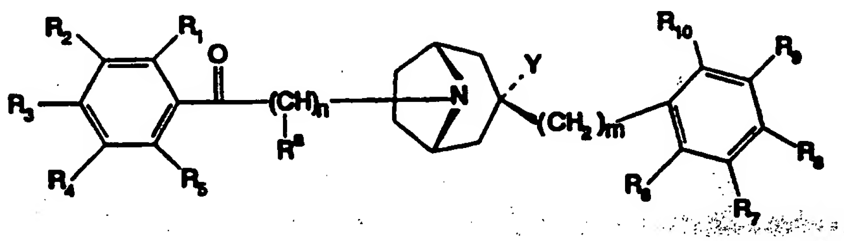


V

wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy or carboxy; and

n is 1 to 5.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*VI*):



VI

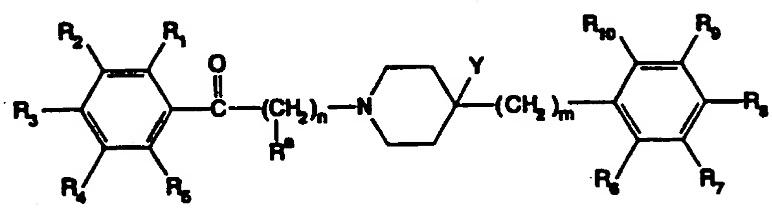
wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; n is 1 to 5,

m is 0 to 3,

Y is one of OH, H, CN, CHO, $CONH_2$, CO-alkyl, CO-alkenyl, CH_2NHCO-alkyl, O-alkyl or CO_2-alkyl; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*VII*):



VII

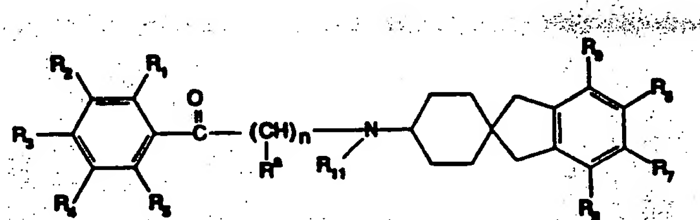
wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; n is 1 to 5,

m is 0 to 3,

Y is one of OH, H, CN, CHO, $CONH_2$, CO-alkyl, CO-alkenyl, CH_2NHCO-alkyl, O-alkyl or CO_2-alkyl; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*VIII*):



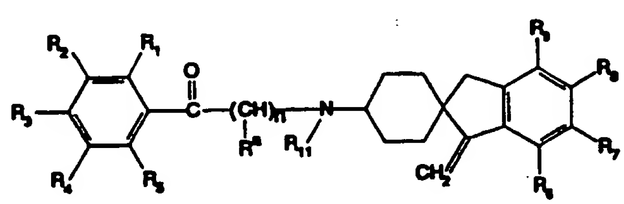
VIII

R_1 to R_9 are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is one of hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*IX*):



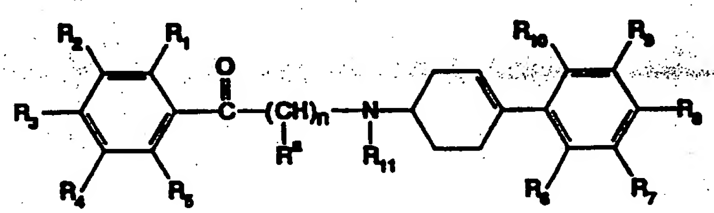
IX

R_1 to R_9 are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*X*):



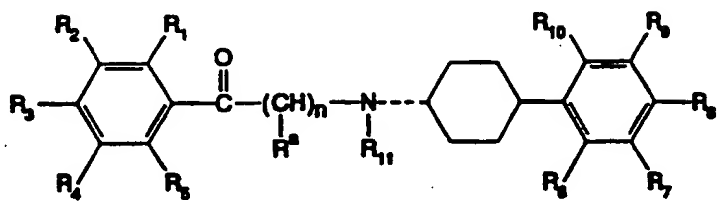
X

R_1 to R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is one of hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XI*):



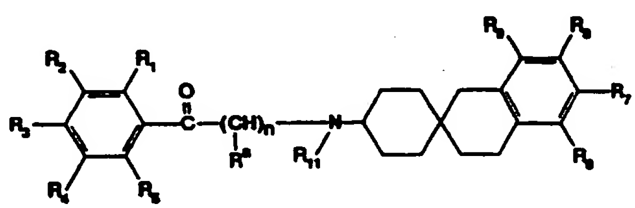
XI

R_1 to R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is one of hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XII*):



XII

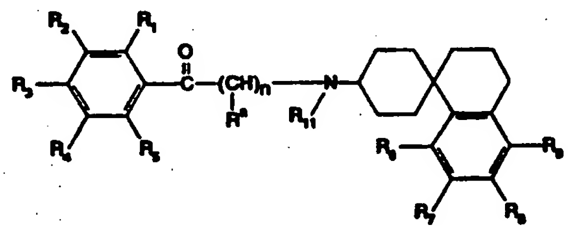
R_1 to R_9 are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is hydrogen, aryl, fused aryl, a heterocyclic group, a

heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XIII*):



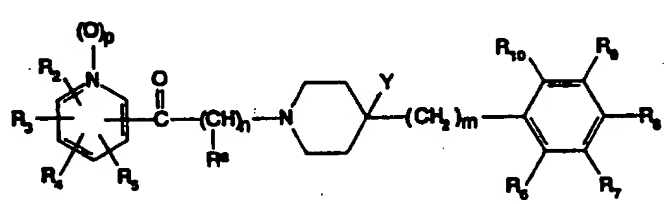
XIII

R_1 to R_9 are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XIV*):



XIV

R_2 to R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

m is 0 to 3;

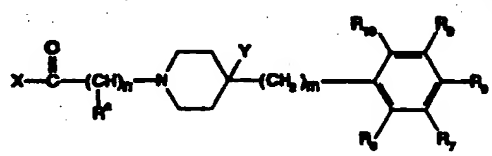
n is 1 to 5;

p is 0 or 1; and

Y is one of OH, H, CN, CHO, $CONH_2$, CO-alkyl, CO-alkenyl, CH_2NHCO-alkyl, O-alkyl or CO_2-alkyl; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (*XV*):



XV

wherein X is an aryl or heteroaryl ring which may be substituted by one or more halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol groups;

m is 0 to 3;

n is 1 to 5;

Y is one of OH, H, CN, CHO, $CONH_2$, CO-alkyl, CO-alkenyl, CH_2NHCO-alkyl, O-alkyl or CO_2-alkyl; and

R^a can vary with each repetitive CH group and is independently hydrogen, alkyl, aryl, hydroxy, or carboxy.

The invention also relates to a method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Down's syndrome, treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, treating anxiety, convulsions, chronic pain, treating migraine headaches, including migraines caused by cortical spreading depression (CSD), treating glaucoma, inducing anesthesia, as well as enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound having one of Formulas ***I-XV***, or a pharmaceutically acceptable salt thereof.

Brief Description of the Figures

Fig. 1 depicts sample records illustrating inhibition of NMDA receptor currents by haloperidol in an oocyte expressing the NR1A/2B subtype.

Fig. 2 depicts concentration-inhibition curves comparing the sensitivities of four subunit combinations of cloned NMDA receptors to haloperidol. -●- NR1A/2A (n = 3); -▲- NR1A/2B (n = 5); -■- NR1A/2C (n = 3); -◆- NR1A/2D (n = 3).

Figs. 3A and 3B depicts the effects of haloperidol on concentration-response curves for glycine and glutamate at NR1A/2B subunit combinations. Fig. 3A: ○ control (n = 3); ■ + 5 μM haloperidol (n = 3); control EC_{50} = 0.25 ± 0.01 μM; + haloperidol EC_{50} = 0.19 ± 0.03 μM. Fig. 3B: □ control (n = 3); ■ + 5 μM haloperidol (n = 3); control EC_{50} = 1.61 ± 0.15 μM; + haloperidol EC_{50} = 1.04 ± 0.02 μM.

Fig. 4 depicts the haloperidol inhibition of NR1A/2B responses measured at different holding potentials. [gly] = 10 μM, [glutamate] = 100 μM, [haloperidol] = 3 μM. Insets - sample records at -100, -70, -40 and +10mV as indicated.

Fig. 5 depicts the kinetics of inhibition at NR1A/2B.

Fig. 6 depicts the concentration-inhibition curves comparing potencies of haloperidol, haloperidol analogs and related compounds at NR1A/2B subunit combinations. ● haloperidol (n = 5); ■ 2 (n = 4); ▲ 5 (n = 3); ▼ 3 (n = 3); ◆ 6 (n = 3); + 7-trifluperidol (n = 3); × 8-ifenprodil (n = 3).

Fig. 7 depicts concentration-inhibition curves for 2 at four NMDA receptor subtypes. -●- NR1A/2A (n = 3); -▲- NR1A/2B (n = 4); -■- NR1A/2C (n = 3); -◆- NR1A/2D (n = 3).

Fig. 8 depicts concentration-inhibition curves for trifluperidol at four NMDA receptor subtypes. -●- NR1A/2A (n = 3); -▲- NR1A/2B (n = 3); -■- NR1A/2C (n = 3); -◆- NR1A/2D (n = 3).

Fig. 9 depicts concentration-inhibition curves for ifenprodil at four NMDA receptor subtypes. -●- NR1A/2A (n = 3); -▲- NR1A/2B (n = 3); -■- NR1A/2C (n = 3); -◆- NR1A/2D (n = 3).

Fig. 10 concentration-effect curves for 13 at four NMDA receptor subtypes. -●- NR1A/2A (n = 3); -▲- NR1A/2B (n = 2); -■- NR1A/2C (n = 3); -◆- NR1A/2D (n = 3).

Detailed Description of the Preferred Embodiments

We were somewhat dubious that haloperidol acts as partial agonist/antagonist at NMDA receptor glycine sites (Fletcher & MacDonald, *Eur. J. Pharmacol. 235*:291-295 (1993)), because the molecule has no obvious structural similarities with other known NMDA receptor glycine site agonists or antagonists. Nevertheless, the result was of sufficient interest to warrant further investigation, and it was reasoned that haloperidol might serve as a lead compound for a completely novel class of glycine site antagonists. These types of compounds were potentially attractive because haloperidol is active following oral administration and does not appear to have the bioavailability problems associated with many glycine site antagonists. In addition, the earlier report provided evidence that haloperidol

could show *in vivo* efficacy as a neuroprotectant (MacDonald and Johnston, *Synapse* *6*:179-188 (1990)). However, in order to develop a drug with any therapeutic potential it would be necessary to make appropriate modifications to the structure of haloperidol to improve potency at NMDA receptors and, equally important, to increase selectivity with respect to other pharmacologically active sites. In particular, it would be necessary to modify the molecule in such a way as to diminish actions at dopamine receptors, σ-sites and perhaps other catecholaminergic systems.

To begin to explore these possibilities, electrophysiological assays were utilized to characterize the actions of haloperidol at NMDA receptors expressed in *Xenopus* oocytes. Haloperidol was assayed at four subunit combinations of cloned rat NMDA receptors, corresponding to four putative NMDA receptor subtypes (Moriyoshi *et al.*, *Nature (Lond.)* *354*:31-37 (1991); Monyer *et al.*, *Science (Washington, D.C.)* *256*:1217-1221 (1992); Kutsuwada *et al.*, *Nature (Lond.)* *358*:36-41 (1992); Sugihara *et al.*, *Biochem. Biophys. Res. Comm.* *185*:826-832 (1992)).

Using fixed saturating concentrations of agonists (glutamate 100 μM, glycine 1-10 μM depending on subunit combination), inhibitory potency of haloperidol was assayed at NMDA receptors assembled from NR1A/2A, NR1A/2B, NR1A/2C and NR1A/2D subunit combinations (Fig. 1). Unexpectedly, these experiments revealed that haloperidol is a highly selective antagonist for the NR1A/2B combination (IC_{50} ~3 μM), and is at least 50 times less active at NR1A/2A, NR1A/2C and NR1A/2D (Fig. 2) (1, Table 1). The slope of the concentration-inhibition curve was ~1, giving no indication of a mixed population of receptors. Limited solubility of haloperidol in frog Ringer prevented the use of the drug at concentrations >100 μM. However, at this high concentration it appeared that levels of inhibition were already saturating at ~90%, suggesting that inhibition of the response by haloperidol is incomplete. Haloperidol was also tested against putative homooligomeric NR1A receptors expressed in oocytes. The IC_{50} in this case was ~100 μM, suggesting that NR1A subunits alone can generate

haloperidol binding sites but that these sites are under strong allosteric constraints from co-assembled NR2 subunits. More specifically, NR2A, 2C, and 2D subunits would appear to cause reductions in sensitivity to haloperidol, as compared to the homooligomeric NR1A receptors, whereas NR2B subunits cause a 30-fold increase in sensitivity.

The initial study on cultured hippocampal neurons reported that concentration-inhibition curves for haloperidol were shifted rightwards by raising the concentration of glycine; an effect consistent with competitive inhibition at the glycine site (Fletcher and MacDonald, *Eur. J. Pharmacol.* *235*:291-295 (1993)). If inhibition of NR1A/NR2B involved a competitive interaction at the glycine site then concentration-response curves for glycine should be similarly transposed by a fixed concentration of haloperidol (5 μM). Contrary to this, we found that inhibition was essentially unsurmountable and, if anything, was associated with modest reductions in the EC_{50} for glycine; i.e., the opposite of what would be expected for a competitive antagonist (Fig. 3A). To test for possible interactions of haloperidol at glutamate binding sites, the effects of a fixed concentration of haloperidol (5 μM) was assayed on concentration-response curves for glutamate. As described for glycine, inhibition was unsurmountable and involved slight reductions in EC_{50} for glutamate (Fig. 3B). Taken together, these results suggest that haloperidol antagonizes the NR1A/2B receptors through interactions at sites that are distinct from both the agonist and co-agonist binding sites.

To test whether inhibitory effects of haloperidol showed any voltage-dependence, levels of inhibition induced by haloperidol was measured at different holding potentials. Over the range -10 to -110 mV levels of inhibition induced by 3 μM haloperidol on NR1A/2B, the responses (10 μM glycine and 100 μM glutamate) appeared to be largely independent of voltage (Fig. 4). Insensitivity to voltage argues that haloperidol binding sites are not situated deep within the channel pore, where ligand binding could be

affected by the electrical field of the membrane and the passage of ions through the channel.

Studying the kinetics of haloperidol binding using the oocyte preparation is restricted by the speed at which drugs can be applied to the oocyte surface. Under most circumstances uniform drug application takes at least 500 msec, limiting one's ability to resolve the more rapid binding events. Nevertheless, comparing timecourses of inhibition after pretreatment or with simultaneous application of 10-30 μM haloperidol indicated that the drug is able to bind NMDA receptors in the absence of channel activation (Fig. 5). At lower concentrations of haloperidol (e.g. 3 μM) the situation appears to be more complex, and is suggestive of an allosteric inhibitor, the affinity of which is enhanced by the presence of agonist. Even under these conditions, there was no indication of conventional use-dependent channel blocking effects, i.e. during a prolonged incubation in haloperidol there are no increases in levels of inhibition upon repeated applications of agonist.

These results suggest that haloperidol is not a conventional channel blocker. Inhibition by PCP-site ligands (e.g. phencyclidine (PCP), dizozilpine (MK-801) and ketamine) is characterized by strong voltage-dependence and pronounced use-dependence (Honey *et al.*, *Neurosci. Lett.* *61*:135-139 (1985); MacDonald *et al.*, *J. Neurophysiol.* *58*:251-226 (1987); Huettner and Bean, *Proc. Natl. Acad. Sci. USA* *85*:1307-1311 (1988)).

Contrary to the initial study (Fletcher and MacDonald, *Eur. J. Pharmacol.* *235*:291-295 (1993)), no evidence was found that haloperidol is a competitive antagonist/partial agonist at NMDA receptor glycine binding sites or, for that matter, at glutamate sites. One possible explanation for this discrepancy is that cultured hippocampal neurons express NMDA receptors assembled from both NR1A/2A and NR1A/2B subunit combinations, or from more complex subunit compositions with similar resultant pharmacology. Separate studies have shown that NR1A/2A combinations have distinctly lower affinity for glycine than NR1A/2B – EC_{50} values are typically 1-2 μM for NR1A/2A as compared to ~0.2 μM for NR1A/2B (Monyer *et al.*, *Science*

(Washington, D.C.) *256*:1217-1221 (1992); Kutsuwada *et al.*, *Nature (Lond.)* *358*:36-41 (1992)). Thus, in low concentrations of glycine (e.g. 0.3 μM), the NR1A/2A receptors will be weakly activated and responses will be predominantly mediated by NR1A/2B subunit combinations; i.e. receptors that are sensitive to haloperidol. In higher concentrations of glycine (e.g. 10 μM) both NR1A/2B and NR1A/2A combinations will be fully activated. The NR1A/2A receptors are largely insensitive to haloperidol so concentration-inhibition curves repeated under these conditions will tend to be shifted to the right, an effect resembling competitive inhibition. Similar rightward shifts in concentration-response curves for glycine have also been recorded using ifenprodil (see below), but in this case a high sensitivity noncompetitive component was also detected (Legendre and Westbrook, *Mol. Pharmacol.* *40*:289-298 (1991)).

To begin to explore the structure-activity relationship for this action of haloperidol, the molecule was considered as comprised of two potentially active components; a 4-(4-chlorophenyl)-4-hydroxypiperidine structure and a 4-fluorophenyl group, coupled together by a 1-butanone linkage. Molecules corresponding to, or related to, these components were either commercially available (e.g. Research Biochemicals Inc.), or were synthesized (see below).

(1) 2 (4-(4-Chlorophenyl)-4-hydroxypiperidine) was active at NR1A/2B, but it was a relatively weak antagonist, approximately 25 times less potent than haloperidol itself (Fig. 6) (Table 1). Moreover, 2 retained only modest levels of subunit-selectivity. Compared to effects at NR1A/2B, 2 was only 3 times less potent as an inhibitor at NR1A/2A, 5 times less potent as an inhibitor of NR1A/2C, and 9 times less potent as an inhibitor of NR1A/2D (Fig. 7) (Table 1). As described for haloperidol, inhibitory effects of 2 at NR1A/2B were unsurmountable with respect to glycine and glutamate.

(2) 3 (3-(4-fluorobenzoyl)propionic acid), a carboxylic analog of the 4-fluorobutyrophenone portion of haloperidol, was essentially inactive as an

inhibitor at NR1A/2B and was also inactive at NR1A/2A and NR1A/2C (Table 1).

(3) In contrast, 4 (4-chloro-4'-fluorobutyrophenone), a molecule more closely related to the 4-fluorobutyrophenone portion of haloperidol, did show inhibitory effects. As described for 2, inhibition by 4 was characterized by low potency and low selectivity (Table 1).

The results with 2, 3 and 4 give two possible insights into the structure-activity relationship:

(i) That the selectivity and potency of haloperidol at NR1A/2B is dependent upon a combination of *both* the 4-(4-chlorophenyl)-4-hydroxypiperidine and the 4-fluorobutyrophenone portions of the molecule; i.e. upon the structural integrity of the molecule as a whole.

(ii) That some underlying inhibitory properties of haloperidol at NMDA receptors could be found in both the 4-(4-chlorophenyl)-4-hydroxypiperidine and the 4-fluorobutyrophenone portions of the molecule. However, we need to be cautious in this latter interpretation because there remains the possibility that dismantling haloperidol generates molecules that resemble the parent compound in being able to block NMDA receptors but do so through distinctly different mechanisms. Inactivity of 3 is presumably due to the charge-bearing carboxylic acid group which does not appear to be tolerated by the binding site.

These results prompted the assay of three additional structurally related and commercially available molecules: 5 ((±)-4-[-4-(4-chlorophenyl)-4-(4-hydroxypiperidinyl]-4-fluorophenyl-1-butanol), a reduced form of haloperidol; 6 (4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-4-(chlorophenyl)-1-butanone), a chloro-analogue of haloperidol; and 7 (trifluperidol), another clinically used anti-psychotic (Table 1).

Both 5 and 6 were comparatively weak inhibitors of NR1A/2B, respectively 25 times and 45 times less potent that haloperidol itself (Fig. 6). Furthermore, like 2, both compounds were relatively non-selective (Table 1). For example, compared to effects at NR1A/2B, 5 had roughly equal potency

as an inhibitor at NR1A/2A and was only 3 times less potent as an inhibitor of NR1A/2C. NR1A/2D receptors were only weakly blocked at concentrations of up to 100 μM.

Trifluperidol, on the other hand, appeared to be slightly more potent than haloperidol as an inhibitor of NR1A/2B (Fig. 6) (Table 1). In terms of subtype specificity, trifluperidol also retained clear selectivity for NR1A/2B, though this was not as pronounced as that seen with haloperidol. NR1A/2A subunit combinations were approximately 40 times less sensitive to trifluperidol than NR1A/2B. By extrapolation, NR1A/2C combinations would appear to be ~180 times less sensitive to trifluperidol than NR1A/2B (Fig. 8). It should be noted, however, that using 100 μM trifluperidol there was clear inhibition at NR1A/2A, and also some inhibition at NR1A/2C and NR1A/2D, effects that were not obvious when using haloperidol. As described for haloperidol, inhibition of NR1A/2B by trifluperidol appeared to be noncompetitive with respect to glycine and glutamate.

These results give two further insights into the structure-activity relationship for haloperidol-type molecules at NMDA receptors:

(iii) The low potencies and poor subunit-selectivity of 5 and 6 indicate that relatively modest structural changes in the 4'-fluorobutyrophenone portion of haloperidol can have pronounced effects on inhibition. Most strikingly, simply substituting the 4'-fluoro-group with a 4'-chloro results in a ~50-fold drop in potency at NR1A/2B.

(iv) The slightly increased potency of trifluperidol with respect to haloperidol suggests that modifications to the 4-(4-chlorophenyl)-4-hydroxypiperidine portion of the molecule might be a viable means of increasing the potency of this type of compound while still retaining substantial levels of subtype selectivity.

In February 1993, a separate paper appeared reporting that a

developmental switch occurs in rat brain NMDA receptors which can be detected by changes in sensitivity to the "atypical" NMDA receptor antagonist ifenprodil (8) (Williams *et al.*, *Neuron 10*:267-278 (1993)). As part of the evidence for this switch, the authors used *Xenopus* oocytes to show that NR1A/2A subunit combinations are substantially less sensitive to ifenprodil than NR1A/NR2B, suggesting that a change in subunit expression might underlie the changes in pharmacology. A subsequent, more detailed, study characterized the inhibitory actions of ifenprodil at NR1A/2A and NR1A/2B receptors expressed in oocytes (Williams *et al.*, *Mol. Pharmacol. 44*:851-859 (1993)).

In light of the present results, the apparent similarities between haloperidol and ifenprodil in terms of subunit-selectivity were striking. Furthermore, a comparison of structures revealed that the two molecules also share some common features (Table 1). The published studies only assayed ifenprodil at NR1A/2A and NR1A/2B. For a more complete comparison with haloperidol, the IC_{50} values for ifenprodil were measured at all four subunit combinations.

As reported previously (Williams *et al.*, *Neuron 10*:267-278 (1993)), ifenprodil was a comparatively potent inhibitor at NR1A/2B subunit combinations (IC_{50} ~0.2 μM), approximately 14 times stronger than haloperidol and 9 times stronger than trifluperidol (Fig. 6). Ifenprodil also showed substantial levels of subunit-selectivity (Fig. 9) (Table 1). NR1A/2A subunit combinations were roughly 40 times less sensitive to ifenprodil than NR1A/2B, NR1A/2C combinations 300 times less sensitive and NR1A/2D 500 times less sensitive.

At present, the precise relationship between effects of haloperidol and ifenprodil at NMDA receptors remains unclear. Still, similarities in subunit-selectivity and structure suggested the possibility that the two drugs share common mechanistic features and might even be interacting at overlapping binding sites:

Firstly, the two drugs both show strongest inhibition at NR1A/2B receptors. Ifenprodil also inhibits NR1A/2A receptors, whereas haloperidol is largely inactive, but this apparent discrepancy might simply be a matter of relative potency, and if haloperidol could be applied at higher concentrations (limited by solubility), inhibition at NR1A/2A would be detected. This argument is supported by the results with trifluperidol, which was slightly more potent than haloperidol, and did show appreciable inhibition at NR1A/2A. Secondly, maximum levels of inhibition at NR1A/2B for both drugs is ~90%; i.e. neither drug appears to be able to block NMDA responses completely. Thirdly, inhibition does not show any pronounced voltage-dependence. Fourthly, preliminary kinetics studies indicate that both drugs are able to interact with the receptor without the necessity of channel activation, and that, unlike PCP-site ligands, neither behaves like a conventional open-channel blocker.

To test the possibility that inhibition of NMDA receptors by haloperidol and ifenprodil were mechanistically similar, two compounds that are hybrids of the two molecules were synthesized. These are: 9 (4-(4-benzylpiperidinyl)-4'-fluorobutyrophenone), where the 4'-fluorobutyrophenone portion of haloperidol is connected to the 4-benzylpiperidine portion of ifenprodil; and 10 (4-(4-benzylpiperidinyl)-4'-fluoropropiophenone), which is the same molecule but with one CH_2 removed from the 1-butanone linkage. Also tested was 11 (3-[4-(4-chlorophenyl)-4-hydroxypiperidinyl]-4'-fluoropropiophenone), which is haloperidol with one CH_2 removed from the 1-butanone linkage (an attempt to increase the resemblance between haloperidol and ifenprodil) and 12 (4-benzylpiperidine), a commercially available compound corresponding to the 4-benzylpiperidine component of ifenprodil.

Preliminary assays indicated that 9 has similar potency and subtype selectivity as haloperidol (Table 1). Some inhibition was detectable at NR1A/2A receptors, i.e. the molecule resembled ifenprodil in this respect,

but NR1A/2B receptors were ~25 times more sensitive. NR1A/2C and NR1A/2D were effectively insensitive at concentrations up to 100 μM.

Preliminary assays indicated that **10** is a little less potent than **9** at NR1A/2B receptors, but has a similar subunit-selectivity profile (Table 1).

Surprisingly, **11** was largely or wholly inactive at all subunit combinations (Table 1).

12 was appreciably weaker than **9** and **10**, and was >75 times weaker than ifenprodil. Nevertheless, this component did appear to show a degree of subunit-selectivity, at least in terms of discriminating NR2A or NR2B containing receptors from those containing NR2C or NR2D.

These results suggest some further insights into structure-activity:

The subunit-selectivity of **9** and **10** support the theory that inhibition of NR1A/2B receptors by haloperidol and ifenprodil are mechanistically related.

The inactivity of **11**, particularly at NR1A/2B, suggests that the length of the linkage is critical to maintaining activity in any simple haloperidol analogs developed as NMDA receptor antagonists. In the case of haloperidol/ifenprodil hybrids, results with **9** and **10** suggest that this parameter is not so critical.

The activity of **12**, albeit weak, suggests that some blocking actions of ifenprodil reside in the 4-benzylpiperidine portion of the molecule. However, as with haloperidol, the potency and selectivity of ifenprodil is critically dependent on maintaining the structural integrity of the molecule.

Lastly, our results indicated that **6**, the 4-chlorophenyl analog of haloperidol, was a surprisingly weak and non-selective NMDA receptor antagonist. This prompted us to synthesize and test **13**, the de-fluoro analog of haloperidol. In terms of IC_{50} value, **13** was of roughly equal potency than haloperidol as an inhibitor of NR1A/2B receptors (Table 1). Still, the most striking feature of these experiments was that maximum levels of inhibition were only 30-60%, a distinctly lower efficacy than any of the other ligands tested (Fig. 10). **13**, applied alone, or in combination with either of the co-

agonists (glycine 1-10 μM or glutamate 100 μM) failed to elicit membrane current responses, indicating that the compound is not behaving as a conventional partial agonist at NR1A/2B.

Assays in oocytes expressing NR1A/2A receptors revealed further complexities. At this subunit combination, 13 caused dose-dependent *increases* in membrane current response (Fig. 10). This effect became detectable between 3-10 μM 13, and potentiation reached 30-50% at 100 μM. 13 did not itself elicit any membrane current responses in oocytes expressing NR1A/2A, and did not appreciably increase currents when applied separately with either of the co-agonists (glycine 10 μM or glutamate 100 μM). Potentiation of responses was still evident at saturating concentrations of glycine and glutamate, all of which implies that the drug does not act as a conventional agonist. NR1A/2C and NR1A/2D subunit combinations were largely, or wholly, unaffected by 13 (Table 1, Fig. 10).

These experiments illustrate two additional and potentially very important features of NMDA receptor inhibition via "haloperidol binding sites."

First, by choosing appropriate substitution patterns it should be possible to generate haloperidol-type molecules showing varying degrees of efficacy as NMDA receptor antagonists. The butyrophenone portion of the molecule would appear to play a critical role in determining the efficacy of antagonism. Limited efficacy NMDA receptor antagonists are attractive because such drugs have built-in safety margins; no matter how high the dosage only a certain fraction of the response can be blocked. This could be particularly important for analgesic, anticonvulsant, and anti-psychotic indications, where overdosage of full antagonists would result in sedation. It is also likely that low efficacy NMDA receptor antagonists, particularly those showing subtype-selectivity, will not induce such profound memory deficits as full antagonists.

Second, the haloperidol binding sites on NMDA receptors are able to mediate either inhibition or potentiation of membrane current response.

Which type of effect predominates appears to be dependent upon the subunit composition of the receptors and on the butyrophenone portion of the molecule. This raises the possibility of developing drugs that selectively potentiate particular subtypes of NMDA receptors. Such drugs could show therapeutic potential as cognitive-enhancers in treatments of neurodegenerative conditions such as Alzheimer's disease. In addition, there is potential of developing drugs that selectively potentiate some subtypes of NMDA receptor while simultaneously having inhibitory effects at other subtypes. Such compounds could be important for adjusting imbalances in subtype activity and may have therapeutic potential as psychotropic agents.

The following Table summarizes various NMDA subtypes, the modulation of which are associated with therapeutic efficacy in various conditions:

Table 2

Condition	Subtype
Stroke	NR1/NR2A & 2B
Hypoglycemia	NR1/NR2A & 2B
Neurodegenerative Diseases	NR1/NR2A & 2B
Analgesia	NR1/2D
Anxiety	NR1/2A or 2B
Epilepsy	NR1/2C or 2D
Psychosis	NR1/2A or 2B
Cognitive Enhancers	NR1/2A or 2B

Thus, if one wished to identify a compound disclosed herein which enhances cognition, the compound may be screened against oocytes bearing the NR1/2A and NR1/2B NMDA receptor subtypes (see example 1). If the compound potentiates currents across the oocyte membrane, then the compound is expected to be useful in enhancing cognition. Compounds which are useful for treating or preventing the adverse consequences of stroke, hypoglycemia, neurodegenerative disorders, anxiety, epilepsy or

psychosis, or which induce analgesia, will inhibit the currents across the membranes of the oocyte expressing the respective NMDA receptor subunit indicated in Table 2.

In summary, previous work has shown that haloperidol blocks NMDA responses in cultured mammalian neurons. The present experiments indicate that antagonism of NMDA receptors by haloperidol shows pronounced subtype-selectivity. Of the four subunit combinations tested, only NR1A/2B was sensitive to inhibition.

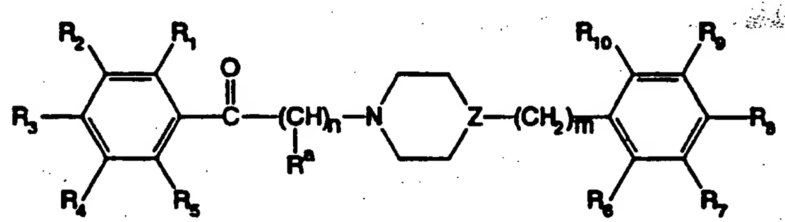
Contrary to a previous report, the present results indicate that haloperidol is not a partial agonist/competitive antagonist at glycine co-agonist sites, is not a competitive antagonist at glutamate agonist sites, and is not a conventional use-dependent channel blocker acting at PCP-sites. Haloperidol appears to be an allosteric inhibitor acting at a distinct, and possibly novel, binding site.

Inhibition of NMDA receptors by haloperidol shares common features with inhibition by the atypical antagonist ifenprodil suggesting that mechanisms of antagonism for these two molecules are related.

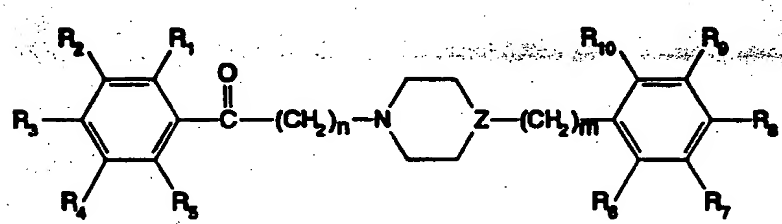
Experiments designed to explore structure-activity relationships for haloperidol at NMDA receptors indicate that subtype-selective inhibition is dependent upon maintaining the basic structural integrity of the molecule. Small modifications in the 4'-fluorobutyrophenone portion of haloperidol can have pronounced effects on the potency, efficacy, and selectivity of inhibition. In particular, removal of the fluorine atom (13) generates a selective low efficacy inhibitor of NR1A/2B receptors that actually potentiates currents mediated by NR1A/2A receptors. On the other hand, modifications to the 4-(4-chlorophenyl)-4-hydroxypiperidine component are one way of increasing potency while retaining subtype selectivity. In particular, trifluperidol is a subtype-selective NMDA receptor antagonist which appears to block NMDA receptors by the same mechanism as haloperidol.

The present invention is also related to the discovery that certain haloperidol analogs have *in vivo* activity as anticonvulsants in MES experiments in mice. For instance, 4-(4-benzylpiperidinyl)butyrophenone hydrochloride (29b) was found to have an ED_{50} of 3.2 mg/kg as an anticonvulsant in mice.

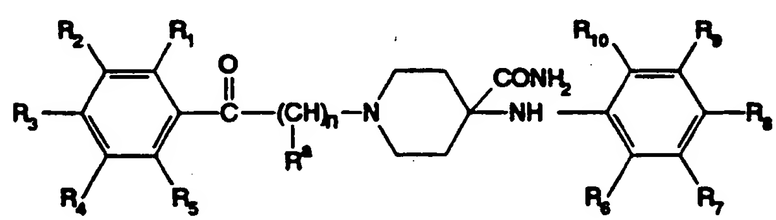
Examples of subtype-selective compounds have the following Formula *I-XV*:



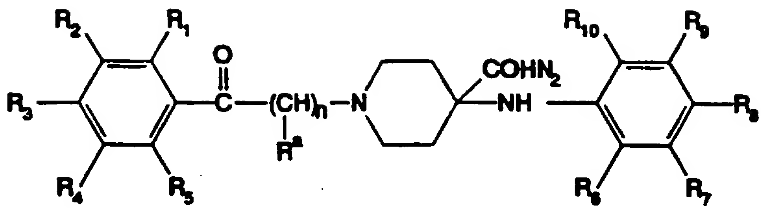
I



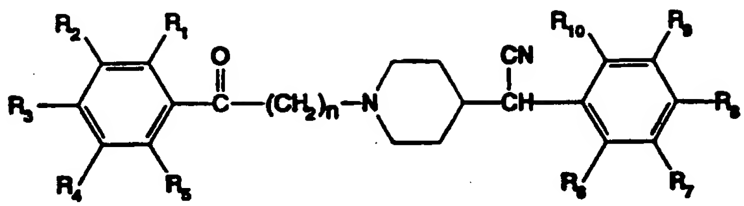
Ia



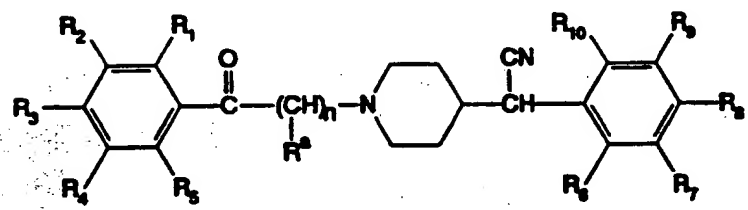
II



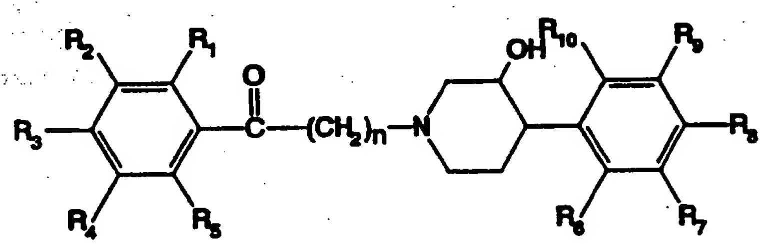
IIa



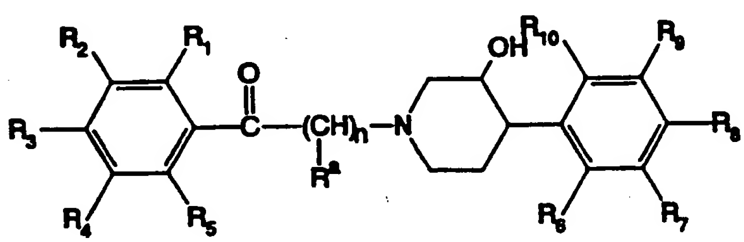
III



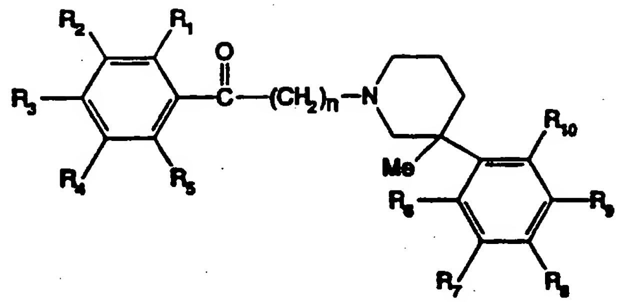
IIIa



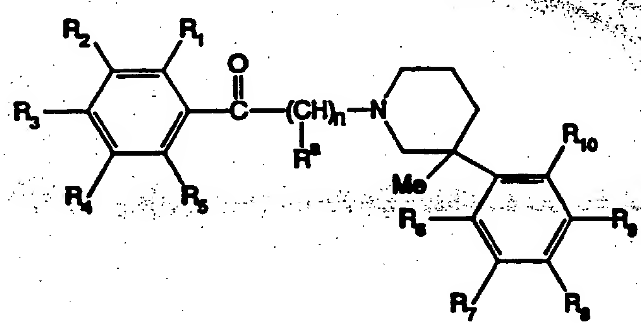
IV



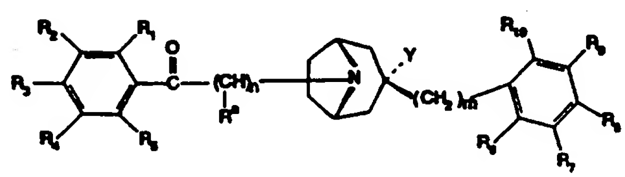
IVa



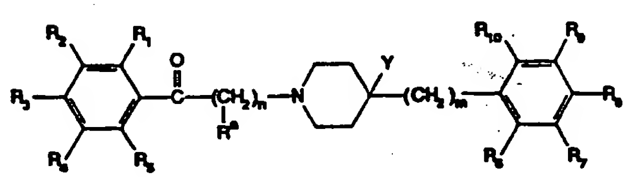
V



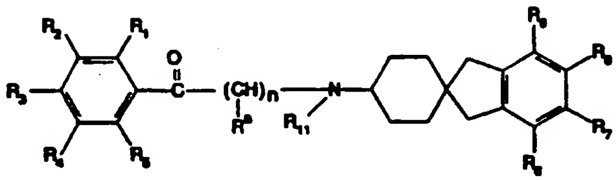
Va



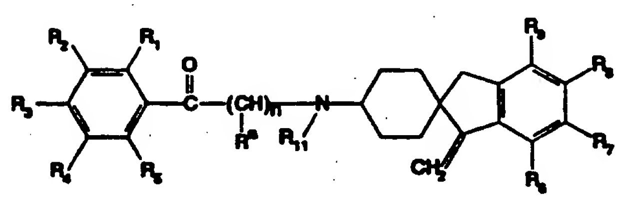
VI



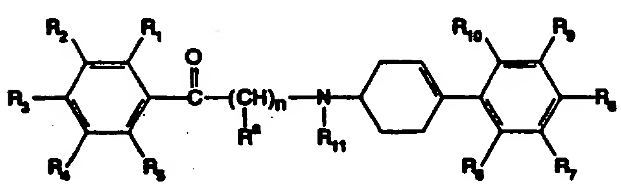
VII



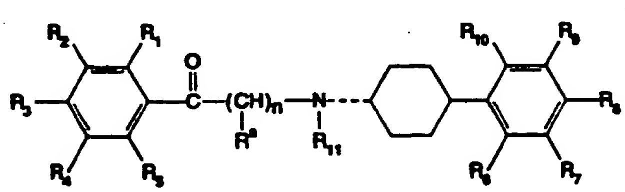
VIII



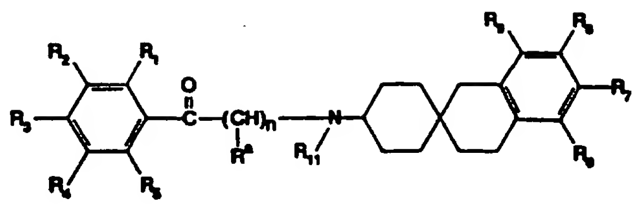
IX



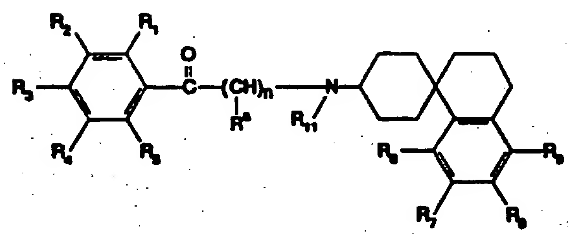
X



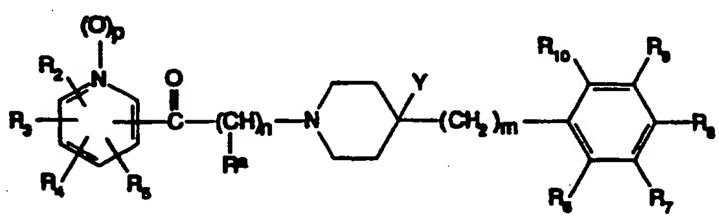
XI



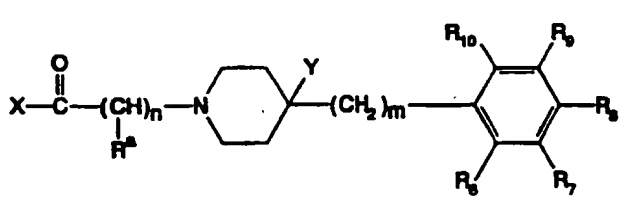
XII



XIII



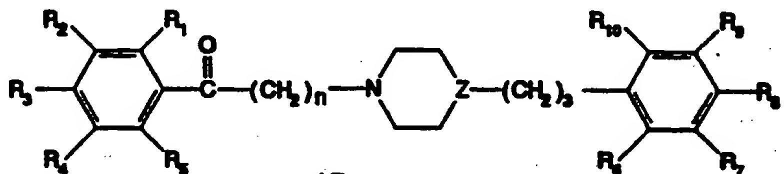
XIV



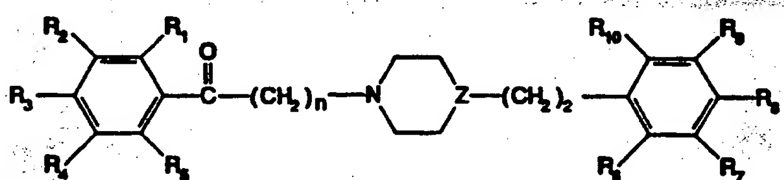
XV

where R_1-R_{11}, R^a, X, Y, Z, n, m and p are each as defined above.

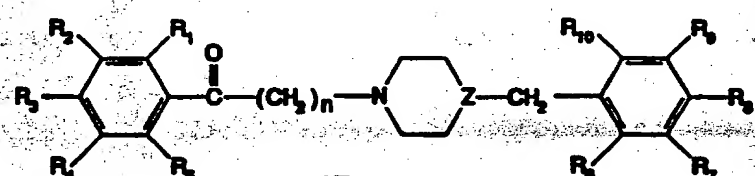
Particular examples of compounds within the scope of Formula ***Ia*** include those having the following formulae:



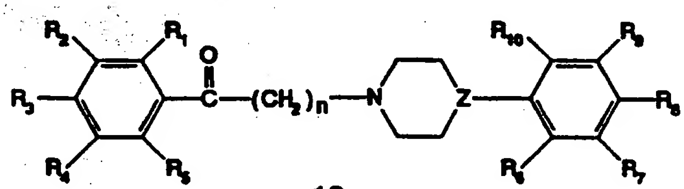
15



16



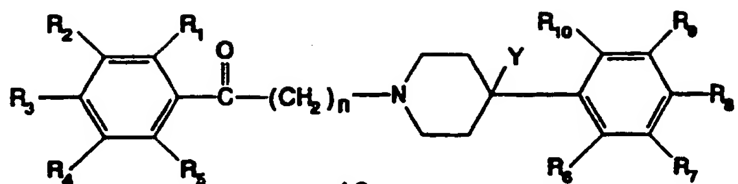
17



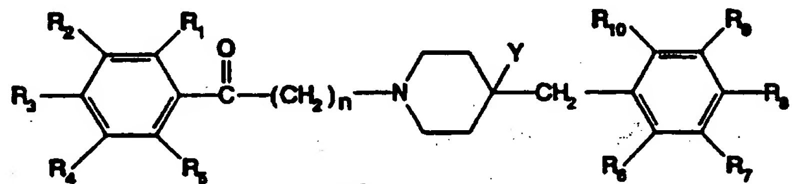
18

where R_1 to R_{10} are as defined above, n is 1 to 5, and Z is as defined above, and is preferably C.

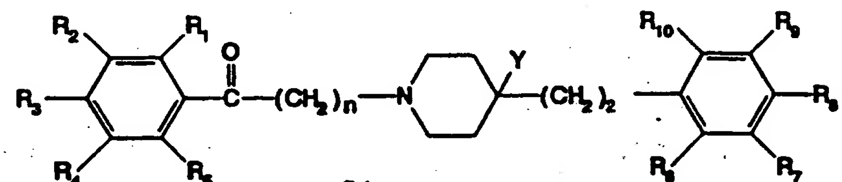
Particular examples of compounds within the scope of Formula ***VII*** include those having the following formulae:



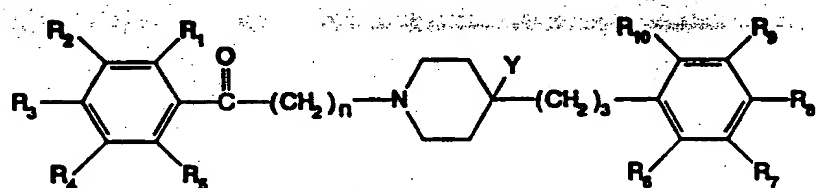
19



20



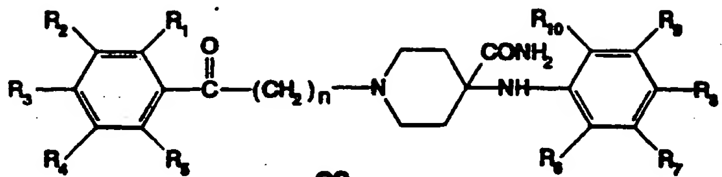
21



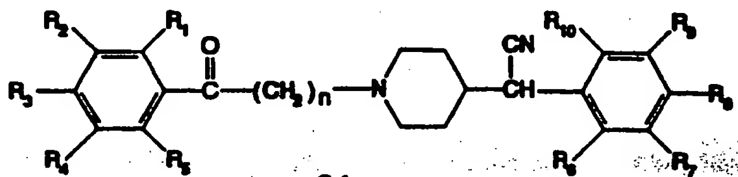
22

where R_1 to R_{10} are as defined above, n is 1 to 5, and Y is one of OH, CN, CHO, $CONH_2$, $COCH_3$, $COCH_2CH_3$, $CH_2NHCOCH_3$, $OCH_2CH_2CH_3$, $COCH_2CH_2CH_3$ or $CO_2CH_2CH{=}CH_2$.

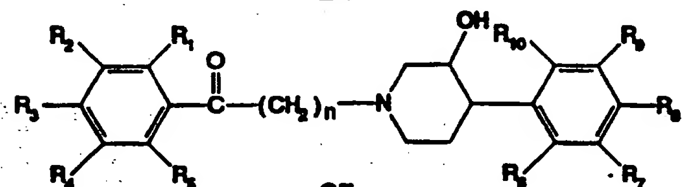
Additional preferred compounds include:



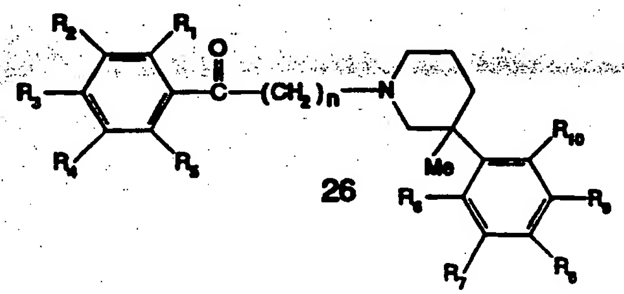
23



24



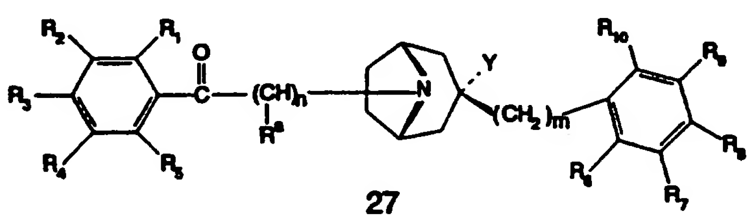
25



26

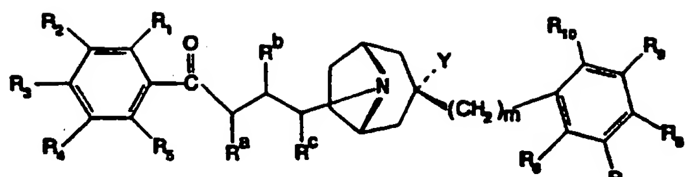
where R_1 to R_{10} are as defined above, and n is 1 to 5.

Other examples include:



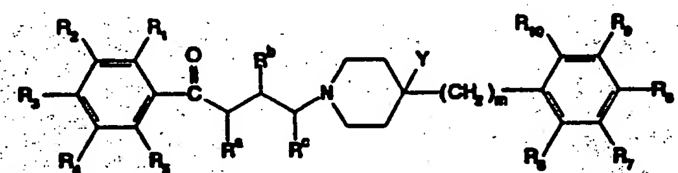
27

where R_1 to R_{10} are as defined above, n is 1 to m is 0 to 3 and Y is as defined above, preferably being hydrogen or hydroxy;



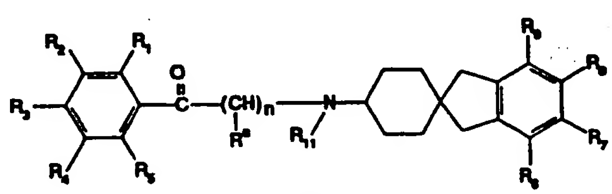
28

where R_1 to R_{10} are as defined above, R^a, R^b, R^c are each independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy, m is 0 to 3, and Y is as defined above, preferably being hydrogen or hydroxy;



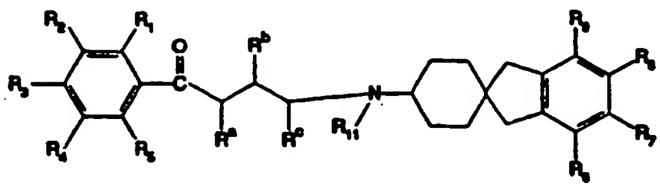
29

where R_1 to R_{10} are as defined above, R^a, R^b, R^c are each independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy, m is 0 to 3, and Y is one of OH, CN, CHO, $CONH_2$, $COCH_3$, $COCH_2CH_3$, $CH_2NHCOCH_3$, $OCH_2CH_2CH_3$, $COCH_2CH_2CH_3$ or $CO_2CH_2CH{=}CH_2$.



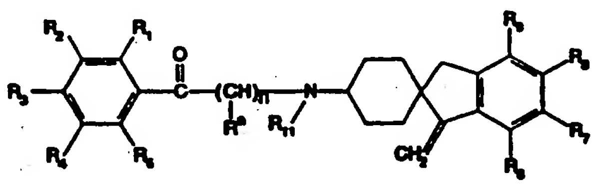
30

where R_1 to R_9 and R_{11} are as defined above and n is 0 to 5;



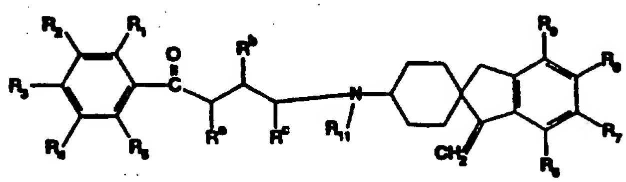
31

where R_1 to R_9 and R_{11} are as defined above, and R^a, R^b, R^c are each independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy;



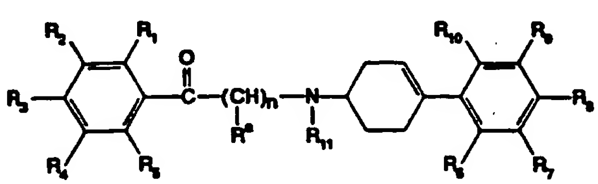
32

where R_1 to R_9 and R_{11} are as defined above, and n is 1 to 5;



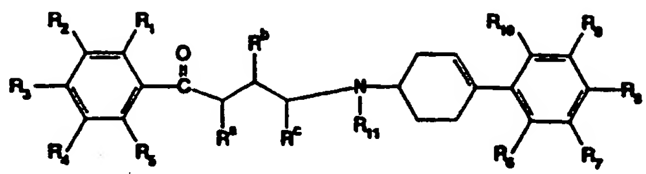
33

where R_1 to R_9 and R_{11} are as defined above, and R^a, R^b, R^c are each independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy;



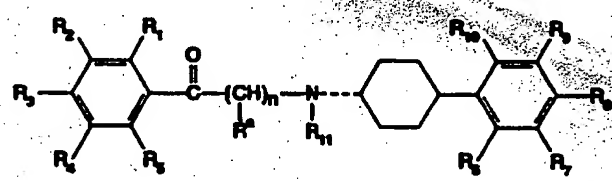
34

where R_1 to R_{11} are as defined above, and n is 1 to 5;



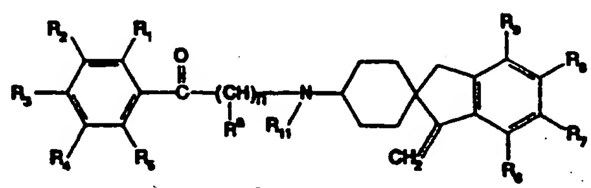
35

where R_1 to R_{11} are as defined above, and R^a, R^b, R^c are each independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy;



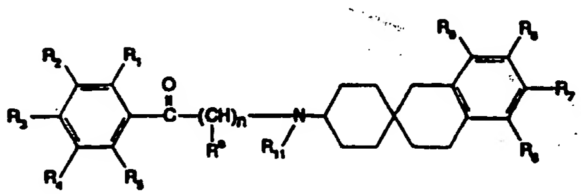
36

where R_1 to R_{11} are as defined above, and n is 1 to 5;



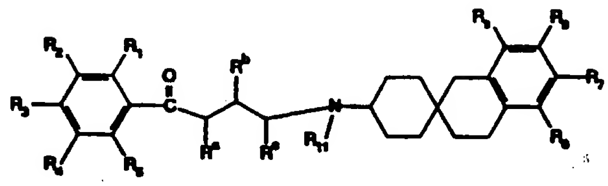
37

where R_1 to R_9 and R_{11} are as defined above, and R^a, R^b, R^c are each independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy;



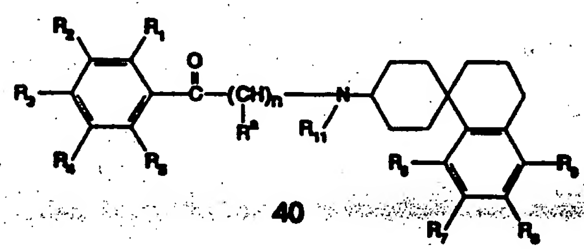
38

where R_1 to R_9 and R_{11} are as defined above, and n is 0 to 5;



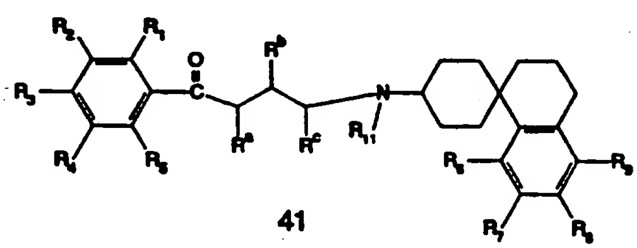
39

where R_1 to R_9 and R_{11} are as defined above, and R^a, R^b, R^c are each independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy;



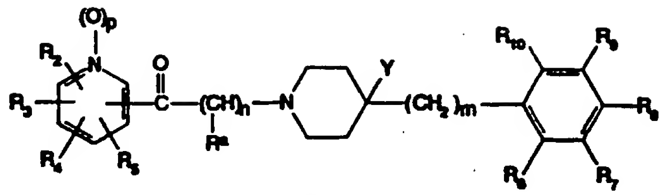
40

where R_1 to R_9 and R_{11} are as defined above, and n is 0 to 5;



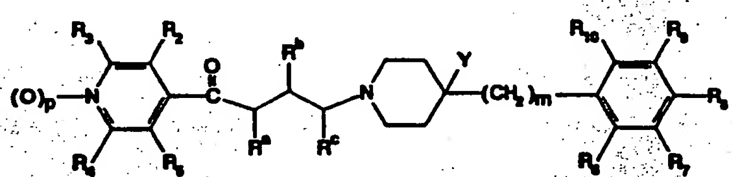
41

where R_1 to R_9 and R_{11} are as defined above, and R^a, R^b, R^c are each independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy;



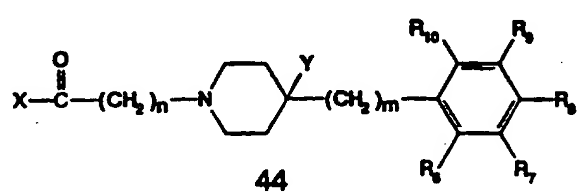
42

where R_2 to R_{10} are as defined above, n is 0 to 5, m is 0 to 3, p is 0 or 1, and Y is one of OH, CN, CHO, $CONH_2$, $COCH_3$, $COCH_2CH_3$, $CH_2NHCOCH_3$, $OCH_2CH_2CH_3$, $COCH_2CH_2CH_3$ or $CO_2CH_2CH{=}CH_2$.



43

where R_2 to R_{10} are as defined above, R^a, R^b, R^c are each independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy, m is 0 to 3, p is 0 or 1 and Y is one of OH, CN, CHO, $CONH_2$, $COCH_3$, $COCH_2CH_3$, $CH_2NHCOCH_3$, $OCH_2CH_2CH_3$, $COCH_2CH_2CH_3$ or $CO_2CH_2CH{=}CH_2$.



44

where R_6 to R_{10} are as defined above, X is as defined above, n is 1 to 5, m is 0 to 3 and Y is one of CN, CHO, $CONH_2$, $COCH_3$, $COCH_2CH_3$, $CH_2NHCOCH_3$, $OCH_2CH_2CH_3$, $COCH_2CH_2CH_3$ or $CO_2CH_2CH{=}CH_2$.

Preferred values of R_1-R_{10} include hydrogen, halo, C_{1-4}haloalkyl, phenyl, benzyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, hydroxy(C_{1-4})alkyl, nitro, amino, cyano, hydroxy, thiol, azido, C_{1-4}alkoxy, C_{1-4}carboxy and C_{1-4}alkylthio.

One of R_1-R_5 is most preferably one of fluoro, chloro, bromo, methyl, ethyl, phenyl, benzyl, trifluoromethyl, methoxy, nitro and the remaining R_1-R_5 are each hydrogen. Most preferred values of R_6-R_{10} include hydrogen, chloro, fluoro, methyl, methoxy, trifluoromethyl, ethyl, phenyl, benzyl and nitro. Preferred values of R_{11} include hydrogen, phenyl, benzyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, hydroxy(C_{1-4})alkyl and C_{2-6}acyl.

Typical C_{6-14} aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl groups.

Typical halo groups include fluorine, chlorine, bromine and iodine. Typical C_{1-4} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec.*-butyl, and *tert.*-butyl groups. Also contemplated is a trimethylene group substituted on two adjoining positions on any benzene ring of the compounds of the invention.

Typical C_{2-4} alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec.*-butenyl.

Typical C_{2-4} alkynyl groups include ethynyl, propynyl, butynyl, and 2-butynyl groups.

Typical arylalkyl groups include any of the above-mentioned C_{1-4} alkyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Typical arylalkenyl groups include any of the above-mentioned C_{2-4} alkenyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Typical arylalkynyl groups include any of the above-mentioned C_{2-4} alkynyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Typical haloalkyl groups include C_{1-4} alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g. fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl and trichloromethyl groups.

Typical hydroxyalkyl groups include C_{1-4} alkyl groups substituted by hydroxy, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups.

Typical alkoxy groups include oxygen substituted by one of the C_{1-4} alkyl groups mentioned above.

Typical alkylthio groups include sulphur substituted by one of the C_{1-4} alkyl groups mentioned above.

Typical acylamino groups include any C_{1-6}acyl (alkanoyl) substituted nitrogen, e.g. acetamido, propionamido, butanoylamido, pentanoylamido, hexanoylamido as well as aryl-substituted C_{2-6} substituted acyl groups.

Typical acyloxy groups include any C_{1-6} acyloxy groups, e.g. acetoxy, propionoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy and the like.

Typical heterocyclic groups include tetrahydrofuranyl, pyranyl, piperidinyl, piperizinyl, pyrrolidinyl, imidazolindinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl and pyrazolinyl groups.

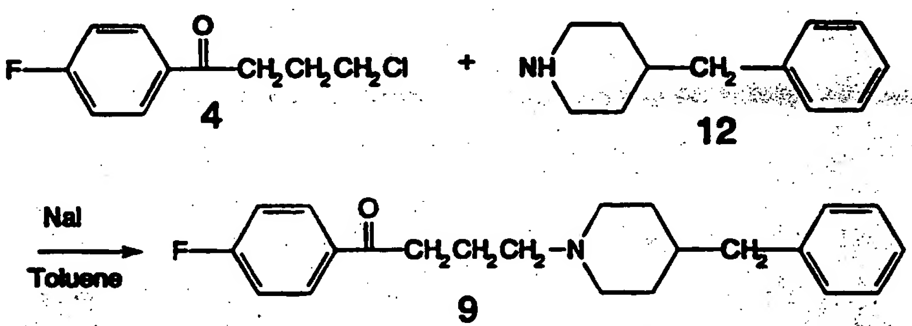
Typical heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, 5a*H*-carbozolyl, carbozolyl, β-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxazinyl groups.

Typical amino groups include $-NH_2$, $-NHR^{14}$, and $-NR^{14}R^{15}$, wherein R^{14} and R^{15} are C_{1-4} alkyl groups as defined above.

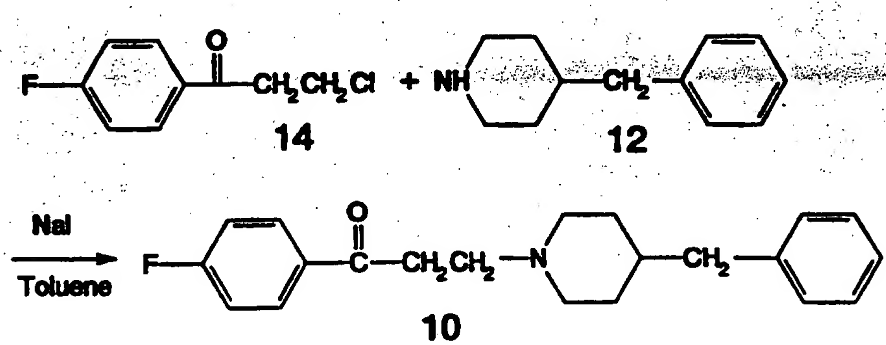
Typical carbonylamido groups are carbonyl groups substituted by $-NH_2$, $-NHR^{14}$, and $-NR^{14}R^{15}$ groups as defined above.

These compounds may be prepared following the general procedure as described by Janssen *et al.* (*J. Med. & Pharm. Chem. 1*:281 (1959)) by coupling of the substituted piperidines or piperazines with the substituted ω-haloalkylphenones (see examples below).

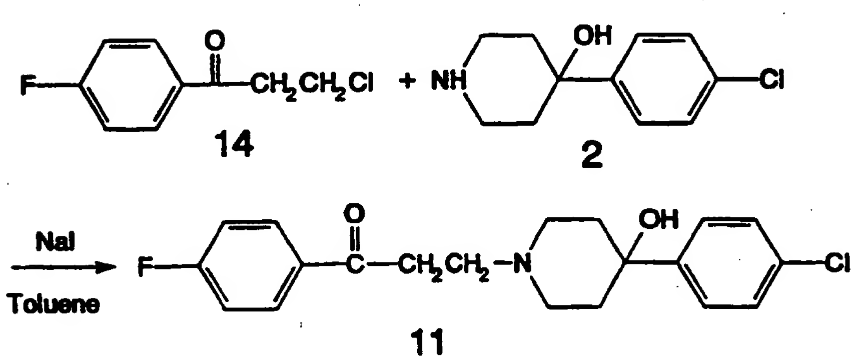
Compounds 9 and 10 were prepared by coupling of 4-benzylpiperidine (12) with 4-chloro-4'-fluorobutyrophenone (4) and 3-chloro-4'-fluoropropiophenone (14), respectively (eq 1 and 2). Compound 11 was prepared by coupling of 4-(4-chlorophenyl)-4-hydroxypiperidine (2) with 3-chloro-4'-fluoropropiophenone (14) (eq 3).



(1)



(2)



(3)

Particularly preferred haloperidol analogs of the present invention include, but are not limited to 4-[4-(4-chlorophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(4-bromophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(4-methylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(4-ethylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(4-phenylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(4-trifluoromethylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(4-fluorophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(4-methoxyphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(4-nitrophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(3-chlorophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(3-bromophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(3-methylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(3-ethylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(3-phenylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(3-trifluoromethylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(3-fluorophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(3-methoxyphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(3-nitrophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(2-chlorophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(2-bromophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(2-methylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(2-ethylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(2-phenylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(2-trifluoromethylphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(2-fluorophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(2-methoxyphenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(2-nitrophenyl)-4-hydroxypiperidinyl]-butyrophenone, 4-[4-(4-bromophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(4-methylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(4-ethylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(4-phenylphenyl)-4-

hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(4-trifluoromethylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(4-fluorophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(4-methoxyphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(4-nitrophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-bromophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-chlorophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-methylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-ethylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-phenylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-trifluoromethylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-fluorophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-methoxyphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-nitrophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(2-bromophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(2-chlorophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(2-methylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(2-ethylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(2-phenylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(2-trifluoromethylphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(2-fluorophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(2-methoxyphenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-[4-(2-nitrophenyl)-4-hydroxypiperidinyl]-4'-fluorobutyrophenone, 4-(4-benzylpiperidinyl)-4'-fluorobutyrophenone, 4-(4-benzyl-4-hydroxypiperidinyl)-4'-fluorobutyrophenone, 4-[4-(2-phenylethyl)piperidinyl]-4'-fluorobutyrophenone, 4-[4-(3-phenylpropyl)piperidinyl]-4'-fluorobutyrophenone, 4-[4-hydroxy-4-(3-phenylpropyl)piperidinyl]-4'-fluorobutyrophenone, 4-(4-amino-4-phenylpiperidinyl)-4'-fluorobutyrophenone, 4-(4-amino-4-benzylpiperidinyl)-4'-fluorobutyrophenone, 4-[3-hydroxy-4-(3-trifluoromethylphenyl)piperidinyl]-4'-fluorobutyrophenone, 4-(4-cyano-4-phenylpiperidinyl)-4'-

fluorobutyrophenone, 4-(4-carbamyl-4-phenylpiperidinyl)-4'-fluorobutyrophenone, 4-[4-(α-cyanobenzyl)piperidinyl]-4'-fluorobutyrophenone, 4-(4-acetyl-4-phenylpiperidinyl)-4'-fluorobutyrophenone, 4-(4-phenyl-4-propionylpiperidinyl)-4'-fluorobutyrophenone, 4-(4-acetamidomethyl-4-phenylpiperidinyl)-4'-fluorobutyrophenone, 4-(4-phenyl-4-propoxypiperidinyl)-4'-fluorobutyrophenone, 4-(4-butyryl-4-phenylpiperidinyl)-4'-fluorobutyrophenone, 4-(4-anilino-4-carbamylpiperidinyl)-4'-fluorobutyrophenone, 4-(3-methyl-3-phenylpiperidinyl)-4'-fluorobutyrophenone, 4-[3-(4-chlorophenyl)-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]-4'-fluorobutyrophenone, 4-(3-benzyl-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]-4'-fluorobutyrophenone, 4-{(spiro[cyclohexane-1,2'-indan]-4-yl)amino}-4'-fluorobutyrophenone, 4-{(1'-methylenespiro[cyclohexane-1,2 '-indan]-4-yl)amino}-4'-fluorobutyrophenone, 4-(4-phenylcyclohex-3-en-1-ylamino)-4'-fluorobutyrophenone, 4-(4-phenylcyclohexylamino)-4'-fluorobutyrophenone, 4-{(3'4'-dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-yl)amino}-4'-fluorobutyrophenone, 4-{(3'4'-dihydrospriro[cyclohexane-1,1'(2'*H*)-naphthalen]-4-yl)amino}-4'-fluorobutyrophenone, 4-[4-(4-chlorophenyl)-4-hydroxypiperidinyl]-1-(4-pyridinyl)-1-butanone, 4-[4-(4-chlorophenyl)-4-hydroxypiperidinyl)-1-[4-(N-oxy)pyridinyl]-1-butanone, 4-[4-(4-chlorophenyl)-4-hydroxypiperidinyl)-3-phenyl-4'-fluorobutyrophenone, 4-(4-benzylpiperidinyl)butyrophenone, 4-(4-benzyl-4-hydroxypiperidinyl)butyrophenone, 4-[4-(2-phenylethyl)piperidinyl]butyrophenone, 4-[4-(3-phenylpropyl)piperidinyl]butyrophenone, 4-[4-hydroxy-4-(3-phenylpropyl)piperidinyl]butyrophenone, 4-(4-amino-4-phenylpiperidinyl)butyrophenone, 4-(4-amino-4-benzylpiperidinyl)butyrophenone, 4-[3-hydroxy-4-(3-trifluoromethyl)piperidinyl]butyrophenone, 4-(4-cyano-4-phenylpiperidinyl)butyrophenone, 4-(4-carbamyl-4-

phenylpiperidinyl)butyrophenone, 4-[4-α-cyanobenzyl)piperidinyl]butyrophenone, 4-(4-acetyl-4-phenylpiperidinyl)butyrophenone, 4-(4-phenyl-4-propionylpiperidinyl)butyrophenone, 4-(4-acetamidomethyl-4-phenylpiperidinyl)butyrophenone, 4-(4-phenyl-4-propoxypiperidinyl)butyrophenone, 4-(4-butyryl-4-phenylpiperidinyl)butyrophenone, 4-(4-anilino-4-carbamylpiperidinyl)butyrophenone, 4-(3-methyl-3-phenylpiperidinyl)butyrophenone, 4-[3-(4-chlorophenyl)-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]butyrophenone, 4-(3-benzyl-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]butyrophenone, 4-{(spiro[cyclohexane-1,2'-indan]-4-yl)amino}butyrophenone, 4-{(1'-methylenespiro[cyclohexane-1,2'-indan]-4-yl)amino}butyrophenone, 4-(4-phenylcyclohex-3-en-1-ylamino)butyrophenone, 4-(4-phenylcyclohexylamino)butyrophenone, 4-{(3'4'-dihydrospiro[cyclohexane-1,2'(1'*H*)-naphthalen]-4-yl)amino}butyrophenone, 4-{(3'4'-dihydrospiro[cyclohexane-1,1'(2'*H*)-naphthalen]-4-yl)amino}butyrophenone, 4-[4-(4-chlorophenyl)-4-hydroxypiperidinyl]-3-phenylbutyrophenone, 4-(4-benzylpiperidinyl)-4'-fluoropropiophenone, 4-(4-benzyl-4-hydroxypiperidinyl)-4'-fluoropropiophenone, 4-[4-(2-phenylethyl)piperidinyl]-4'-fluoropropiophenone, 4-[4-(3-phenylpropyl)piperidinyl]-4'-fluoropropiophenone, 4-[4-hydroxy-4-(3-phenylpropyl)piperidinyl]-4'-fluoropropiophenone, 4-(4-benzylpiperidinyl)propiophenone, 4-(4-benzyl-4-hydroxypiperidinyl)propiophenone, 4-[4-(2-phenylethyl)piperidinyl]propiophenone, 4-[4-(3-phenylpropyl)piperidinyl]propiophenone, 4-[4-hydroxy-4-(3-phenylpropyl)piperidinyl]propiophenone, 2-[4-(4-chlorophenyl)-4-hydroxypiperidinyl]-4'-fluoroacetophenone, 4-(4-hydroxy-4-phenylpiperidinyl)butyrophenone, and 4-(4-benzylpiperidinyl)-butyrophenone.

Certain of the compounds of the present invention are expected to be potent anticonvulsants in animal models and will prevent ischemia-induced nerve cell death in the gerbil global ischemia model after administration.

The compounds of the present invention are active in treating or preventing neuronal loss, neurodegenerative diseases, chronic pain, migraine headaches, are active as anticonvulsants and inducing anesthesia. They are also useful for treating epilepsy and psychosis. Additionally, the compounds of the present invention are useful for treating glaucoma, including primary open-angle glaucoma, chronic closed-angle glaucoma, as well as other sub-types of glaucoma or ocular hypertension. The therapeutic and side effect profiles of subunit-selective NMDA receptor antagonists and agonists should be markedly different from the more non-selective types of inhibitors. The subtype-selective ligands of the present invention are expected to exhibit little or no untoward side effects caused by non-selective binding with other receptors, particularly, the PCP and glutamate bindings sites associated with the NMDA receptor. In addition, selectivity for different NMDA receptor subtypes will reduce side effects such as sedation that are common to non-subtype-selective NMDA receptor antagonists. The compounds of the present invention are effective in treating or preventing the adverse consequences of the hyperactivity of the excitatory amino acids, e.g. those which are involved in the NMDA receptor system, by preventing the ligand-gated cation channels from opening and allowing excessive influx of Ca^{++} into neurons, as occurs during ischemia.

Neurodegenerative diseases which may be treated with the compounds of the present invention include those selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Down's syndrome.

The compounds of the present invention find particular utility in the treatment or prevention of neuronal loss associated with multiple strokes which give rise to dementia. After a patient has been diagnosed as suffering from a stroke, the compounds of the present invention may be administered

to ameliorate the immediate ischemia and prevent further neuronal damage that may occur from recurrent strokes.

Moreover, the compounds of the present invention are able to cross the blood/brain barrier which makes them particularly useful for treating or preventing conditions involving the central nervous system.

The compounds of the invention find particular utility in treating or preventing the adverse neurological consequences of surgery. For example, coronary bypass surgery requires the use of heart-lung machines which tend to introduce air bubbles into the circulatory system which may lodge in the brain. The presence of such air bubbles robs neuronal tissue of oxygen, resulting in anoxia and ischemia. Pre- or post- surgical administration of the compounds of the present invention will treat or prevent the resulting ischemia. In a preferred embodiment, the compounds of the invention are administered to patients undergoing cardiopulmonary bypass surgery or carotid endarterectomy surgery.

The compounds of the present invention also find utility in treating or preventing chronic pain. Such chronic pain may be the result of surgery, trauma, headache, arthritis, pain from terminal cancer or degenerative diseases. The compounds of the present invention also find particular utility in the treatment of phantom pain that results from amputation of an extremity. In addition to treatment of pain, the compounds of the invention are also expected to be useful in inducing anesthesia, either general or local anesthesia, for example, during surgery.

The compounds of the present invention also find utility in treating headaches, in particular, migraine headaches in mammals. The migraine headaches are typically the result of cortical spreading depression (CSD). In a preferred embodiment of this aspect of the present invention, haloperidol analogs having a comparatively low affinity for the NMDA receptor, that is a binding affinity of about 100-fold less the than the binding affinity of MK-801, are employed to treat headaches. It is expected that these low affinity compounds will possess an advantageous time-course and toxicity profile.

It is especially suited for the treatment of headaches. Specifically, these compounds are expected to have a rapid onset of action, in the range of less than about 30 minutes, and a predictable dose-related duration of action.

The compounds of the present invention also find utility in treating glaucoma. In particular, the compounds reduce glutamate-induced excitotoxicity, thereby reducing the loss of retinal ganglion cells resulting from such excitotoxicity. Thus, this aspect of the present invention is useful for the reduction or prevention of damage to retinal ganglion cells and their axons comprising the optic nerve in glaucomatic subjects. *See*, PCT application No. WO 94/13275, published June 23, 1994.

The subunit-selective NMDA receptor antagonists, agonists and modulators may be tested for *in vivo* anticonvulsant activity after intraperitoneal injection using a number of anticonvulsant tests in mice (audiogenic seizure model in DBA-2 mice, pentylenetetrazol-induced seizures in mice, maximum electroshock seizure test (MES) or NMDA-induced death). The compounds may also be tested in drug discrimination tests in rats trained to discriminate PCP from saline. It is expected that most of the compounds of the present invention will not generalize to PCP at any dose. In addition, it is also expected that none of the compounds will produce a behavioral excitation in locomotor activity tests in the mouse. It is expected that such results will suggest that the subunit-selective NMDA receptor antagonists and agonists of the present invention do not show the PCP-like behavioral side effects that are common to NMDA channel blockers such as MK-801 and PCP or to competitive NMDA antagonists such as CGS 19755.

The subunit-selective NMDA receptor antagonists and agonists are also expected to show potent activity *in vivo* after intraperitoneal injection suggesting that these compounds can penetrate the blood/brain barrier.

Thus, the present invention is directed to compounds having high binding to a particular NMDA receptor subunit and low binding to other sites such as dopamine and other catecholamine receptors, and σ sites. According to the present invention, those compounds having high binding to a particular

NMDA subunit exhibit an IC_{50} of about 100 μM or less in an NMDA subunit binding assay (*see* the Examples). Preferably, the compounds of the present invention exhibit an IC_{50} of 10 μM or less. Most preferably, the compounds of the present invention exhibit an IC_{50} of about 1.0 μM or less.

The anxiolytic activity of any particular compound described herein may be determined by use of any of the recognized animal models for anxiety. A preferred model is described by Jones, B.J. *et al.*, *Br. J. Pharmacol. 93*:985-993 (1988). This model involves administering the compound in question to mice which have a high basal level of anxiety. The test is based on the finding that such mice find it aversive when taken from a dark home environment in a dark testing room and placed in an area which is painted white and brightly lit. The test box has two compartments, one white and brightly illuminated and one black and non-illuminated. The mouse has access to both compartments via an opening at floor level in the divider between the two compartments. The mice are placed in the center of the brightly illuminated area. After locating the opening to the dark area, the mice are free to pass back and forth between the two compartments. Control mice tend to spend a larger proportion of time in the dark compartment. When given an anxiolytic agent, the mice spend more time exploring the more novel brightly lit compartment and exhibit a delayed latency to move to the dark compartment. Moreover, the mice treated with the anxiolytic agent exhibit more behavior in the white compartment, as measured by exploratory rearings and line crossings. Since the mice can habituate to the test situation, naive mice should always be used in the test. Five parameters may be measured: the latency to entry into the dark compartment, the time spent in each area, the number of transitions between compartments, the number of lines crossed in each compartment, and the number of rears in each compartment. The administration of the compounds of the present invention is expected to result in the mice spending more time in the larger, brightly lit area of the test chamber.

In the light/dark exploration model, the anxiolytic activity of a putative agent can be identified by the increase of the numbers of line crossings and rears in the light compartment at the expense of the numbers of line crossings and rears in the dark compartment, in comparison with control mice.

A second preferred animal model is the rat social interaction test described by Jones, B.J. *et al., supra*, wherein the time that two mice spend in social interaction is quantified. The anxiolytic activity of a putative agent can be identified by the increase in the time that pairs of male rats spend in active social interaction (90% of the behaviors are investigatory in nature). Both the familiarity and the light level of the test arena may be manipulated. Undrugged rats show the highest level of social interaction when the test arena is familiar and is lit by low light. Social interaction declines if the arena is unfamiliar to the rats or is lit by bright light. Anxiolytic agents prevent this decline. The overall level of motor activity may also be measured to allow detection of drug effects specific to social behaviors.

The efficacy of the NMDA subunit selective antagonists to inhibit glutamate neurotoxicity in rat brain cortex neuron cell culture system may be determined as follows. An excitotoxicity model modified after that developed by Choi (Choi, D.W., *J. Neuroscience* 7:357 (1987)) may be used to test anti-excitotoxic efficacy of the antagonists. Fetuses from rat embryonic day 19 are removed from time-mated pregnant rats. The brains are removed from the fetuses and the cerebral cortex is dissected. Cells from the dissected cortex are dissociated by a combination of mechanical agitation and enzymatic digestion according to the method of Landon and Robbins (*Methods in Enzymology 124*:412 (1986)). The dissociated cells are passed through a 80 micron nitex screen and the viability of the cells are assessed by Trypan Blue. The cells are plated on poly-D-lysine coated plates and incubated at 37°C in an atmosphere containing 91% O_2/9% CO_2. Six days later, fluoro-d-uracil is added for two days to suppress non-neural cell growth. At culture day 12, the primary neuron cultures are exposed to 100

μM glutamate for 5 minutes with or without increasing doses of antagonist or other drugs. After 5 minutes the cultures are washed and incubated for 24 hours at 37°C. Neuronal cell damage is quantitated by measuring lactate dehydrogenase (LDH) activity that is released into the culture medium. The LDH activity is measured according to the method of Decker *et al.* (Decker *et al.*, *J. Immunol. Methods 15*:16 (1988)).

The anticonvulsant activity of the antagonists may be assessed in the audiogenic seizure model in DBA-2 mice as follows. DBA-2 mice may be obtained from Jackson Laboratories, Bar Harbor, Maine. These mice at an age of <27 days develop a tonic seizure within 5-10 seconds and die when they are exposed to a sound of 14 kHz (sinus wave) at 110 dB (Lonsdale, D., *Dev. Pharmacol. Ther. 4*:28 (1982)). Seizure protection is defined when animals injected with drug 30 minutes prior to sound exposure do not develop a seizure and do not die during a 1 minute exposure to the sound. 21 day old DBA-2 mice are used for all experiments. Compounds are given intraperitoneally in either saline, DMSO or polyethyleneglycol-400. Appropriate solvent controls are included in each experiment. Dose response curves are constructed by giving increasing doses of drug from 1 mg/kg to 100 mg/kg. Each dose group (or solvent control) consists of at least six animals.

The anticonvulsant efficacy of the antagonists may be assessed in the pentylenetetrazol (PTZ)-induced seizure test as follows. Swiss/Webster mice, when injected with 50 mg/kg PTZ (i.p.) develop a minimal clonic seizure of approximately 5 seconds in length within 5-15 minutes after drug injection. Anticonvulsant efficacy of an antagonist (or other) drug is defined as the absence of a seizure when a drug is given 30 minutes prior to PTZ application and a seizure does not develop for up to 45 minutes following PTZ administration. The antagonist or other drugs are given intraperitoneally in either saline, DMSO or polyethyleneglycol-400. Appropriate solvent controls are included in each experiment. Dose response curves are

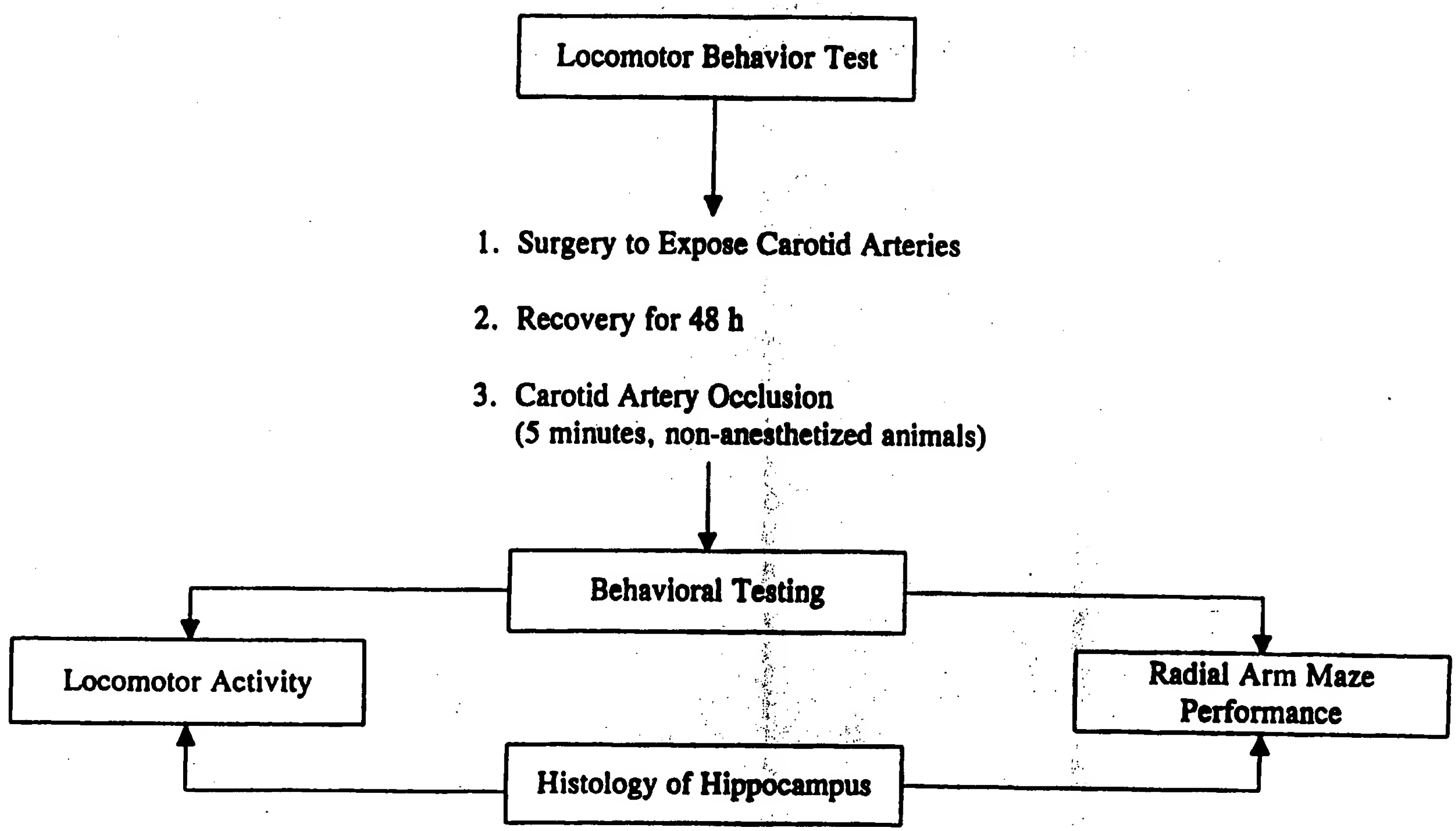
constructed by giving increasing doses of drug from 1 mg/kg to 100 mg/kg. Each dose group (or solvent control) consists of at least six animals.

The efficacy of NMDA antagonists to protect mice from NMDA-induced death may be assessed as follows. When mice are injected with 200 mg/kg N-methyl-D-aspartate (NMDA) i.p., the animals will develop seizures followed by death within 5-10 minutes. The antagonists are tested for their ability to prevent NMDA-induced death by giving the drugs i.p. 30 minutes prior to the NMDA application. The antagonist or other drugs are given intraperitoneally in either saline, DMSO or polyethyleneglycol-400. Appropriate solvent controls are included in each experiment. Dose response curves are constructed by giving increasing doses of drug from 1 mg/kg to 100 mg/kg. Each dose group (or solvent control) consists of at least six animals.

The series of different evaluations may be conducted on doses of the NMDA antagonists of the invention to determine the biological activity of the compounds both in normal gerbils and in animals exposed to 5 minutes of bilateral carotid occlusion. *See* Scheme I.

Scheme I

Gerbil Ischemia Model



These studies are conducted in animals who are conscious and have no other pharmacological agents administered to them. Gerbils are preinstrumented 48-hours prior to ischemia to allow for the complete elimination of the pentobarbital anesthetic which is employed. When tested with drugs, animals are given IP injections of the NMDA antagonist or vehicle. In the case of multiple injections, animals are given IP injections 2 hours apart and the final injection is given 30 minutes prior to the ischemic period or in the case of post treatment, the animals are given injections at 30 minutes, 2 hours, 4 hours and 6 hours post-ischemic reperfusion.

In order to assess the direct pharmacological activity or potential activity of the NMDA antagonists, naive gerbils are injected with either saline or differing doses of the antagonist. The behavioral changes are assessed using a photobeam locomotor activity chamber which is a two foot circular diameter arena with photobeam detection. Animals are individually placed in the 2 foot diameter chambers. The chambers are housed in a cabinet which is closed and noise is abated using both a background white noise generator and a fan. Animals are placed in these chambers in the case of the initial pharmacological evaluation for a period of 6 hours and the total activity during each successive hour is accumulated using the computer control systems.

Saline results in an initial high rate of activity, with the control animals showing a first hour activity level of about 1600 counts. This level of control activity is typical for the gerbil under these experimental conditions. As the session progressed, animals decrease their exploratory activity and at the terminal period the activity declines to about 250 counts per hour. It is expected that the NMDA antagonists of the present invention will have no significant effect on either the initial exploratory rate or the terminal rate of exploration.

In a next phase of the evaluation of the NMDA antagonists, gerbils are pretreated with varying doses of the antagonists and then exposed to a five minute period of bilateral carotid occlusion. Following the initiation of

reperfusion, animals are placed into the circular locomotor activity testing apparatus and the activity at the beginning of the first hour following reperfusion is monitored for the subsequent four hours.

Control animals not exposed to ischemia and given injections of saline prior to being placed in the locomotor activity chamber show a characteristic pattern of activity which in the first hour of locomotor activity is substantially higher than during all other hours and progressively declined over the four hours to a very low value. In contrast to the progressive decline in activity over the four hour testing period, control animals that are exposed to five minutes of cortical ischemia demonstrate a completely different pattern of locomotor activity. During the first hour there is a significant decline in activity which is followed by a progressive increase in which the activity during the fourth hour is ten-fold higher than that demonstrated by animals not exposed to carotid occlusion. These results are typical and are a reliable result of the alterations caused by five minutes of bilateral carotid occlusion in the gerbil.

Separate groups of gerbils are pretreated with the NMDA antagonists of the invention 30 minutes before the onset of carotid occlusion and then placed into the locomotor activity following one hour of reperfusion. It is expected that pretreatment of the gerbils with the NMDA antagonists of the invention will prevent both the post-ischemic decrease and increase in activity. Post-ischemic decreases in activity are expected to be near zero during the first hour following reperfusion. Pretreatment with the NMDA antagonists of the invention is expected to reduce or prevent this early depression of behavior. In addition, the NMDA antagonists of the invention are expected to prevent the post-ischemic stimulation of behavior. Subsequent to completion of the single dose pretreatment evaluations, gerbils are also evaluated with multiple injections of the NMDA antagonists of the invention. Doses are administered I.P. at 6 hours, 4 hours, 2 hours and 30 minutes prior to the onset of 5 minutes of ischemia.

At 24 hours all animals are evaluated for differences in patrolling behavior using a 8-arm radial maze. In this procedure, animals are placed into the center start chamber of the maze, the barrier removed and the amount of time and the number of times the animal makes an error recorded prior to completion of exploration in all 8 arms of the maze. An error is defined as the revisiting of an arm by entering to the extent of the entire body without including tail by the animal. If the animal perseveres or fails to leave the arm for longer than five minutes, the session is terminated. In the control population of the animals, the number of errors and exploration of the maze with no prior experience (naive) is approximately 6 errors. This is an average value for an N of 28 gerbils. Following 5 minutes of bilateral carotid occlusion and testing at 24 hours, gerbils make an average number of errors of 21. When animals are pretreated with the NMDA antagonists of the invention, there is expected to be a significant reduction in the number of errors made. There is also expected to be a significant sparing of the behavioral changes that are induced in the radial arm maze performance.

It is also expected that post treatment with the NMDA antagonists of the invention will reduce the short term memory impairment 24 hours post ischemic/reperfusion.

The effects of 5 minutes of bilateral carotid occlusion on neuronal cell death in the dorsal hippocampus may be evaluated in animals 7 days after ischemia reperfusion injury. Previous studies have demonstrated that neuronal degeneration begins to occur around 3 days following cerebral ischemia. By 7 days those neurons which have been affected and will undergo cytolysis and have either completed degeneration or are readily apparent as dark nuclei and displaced nuclei with eosinophilic cytoplasm with pycnotic nuclei. The lesion with 5 minutes of ischemia is essentially restricted within the hippocampus to the CA1 region of the dorsal hippocampus. The intermedial lateral zone of the horn is unaffected and the dentate gyrus and/or in CA3 do not show pathology. Gerbils are anesthetized on day 7 following ischemia with 60 mg/kg of pentobarbital.

Brains are perfused transcardiac with ice-cold saline followed by buffered paraformaldehyde (10%). Brains are removed, imbedded and sections made. Sections are stained with hematoxylin-eosin and neuronal cell counts are determined in terms of number of neuronal nuclei/100 micrometers. Normal control animals (not exposed to ischemia reperfusion injury) will not demonstrate any significant change in normal density nuclei within this region. Exposure to five minutes of bilateral carotid occlusion results in a significant reduction in the number of nuclei present in the CA1 region. In general, this lesion results in a patchy necrosis instead of a confluent necrosis which is seen if 10 minutes of ischemia is employed. Pretreatment with the NMDA antagonists of the invention are expected to produce a significant protection of hippocampal neuronal degeneration.

It is known that NMDA receptors are critically involved in the development of persistent pain following nerve and tissue injury. Tissue injury such as that caused by injecting a small amount of formalin subcutaneously into the hindpaw of a test animal has been shown to produce an immediate increase of glutamate and aspartate in the spinal cord (Skilling, S.R., *et al.*, *J. Neurosci.* *10*:1309-1318 (1990)). Administration of NMDA receptor blockers reduces the response of spinal cord dorsal horn neurons following formalin injection (Dickenson and Aydar, *Neuroscience Lett.* *121*:263-266 (1991); Haley, J.E., *et al.*, *Brain Res.* *518*:218-226 (1990)). These dorsal horn neurons are critical in carrying the pain signal from the spinal cord to the brain and a reduced response of these neurons is indicative of a reduction in pain perceived by the test animal to which pain has been inflicted by subcutaneous formalin injection.

Because of the observation that NMDA receptor antagonists can block dorsal horn neuron response induced by subcutaneous formalin injection, NMDA receptor antagonists have potential for the treatment of chronic pain such as pain which is caused by surgery or by amputation (phantom pain) or by infliction of other wounds (wound pain). However, the use of conventional NMDA antagonists such as MK-801 or CGS 19755, in

preventing or treating chronic pain, is severely limited by the adverse PCP-like behavioral side effects that are caused by these drugs. It is expected that the NMDA receptor antagonists that are the subject of this invention will be highly effective in preventing chronic pain in mice induced by injecting formalin subcutaneously into the hindpaw of the animals. Because the NMDA receptor antagonists of this invention are expected to be free of PCP-like side effects, these drugs are highly useful in preventing or treating chronic pain without causing PCP-like adverse behavioral side effects.

The effects of the NMDA receptor antagonists of the present invention on pain may be evaluated as follows. Male Swiss/Webster mice weighing 25-35 grams are housed five to a cage with free access to food and water and are maintained on a 12 hour light cycle (light onset at 0800h). The NMDA receptor antagonist is dissolved in DMSO at a concentration of 1-40 and 5-40 mg/mL, respectively. DMSO is used as vehicle control. All drugs are injected intraperitoneally (1 μL/g). The formalin test is performed as described (Dubuisson and Dennis, *Pain 4*:H161-174 (1977)). Mice are observed in a plexiglass cylinder, 25cm in diameter and 30cm in height. The plantar surface of one hindpaw is injected subcutaneously with 20 μL of 5% formalin. The degree of pain is determined by measuring the amount of time the animal spends licking the formalin-injected paw during the following time intervals: 0-5′ (early phase); 5′-10′, 10′-15′ and 15′-50′ (late phase). To test whether the NMDA receptor antagonists prevent pain in the test animals, vehicle (DMSO) or drugs dissolved in vehicle at doses of 1mg/kg to 40mg/kg are injected intraperitoneally 30 minutes prior to the formalin injection. For each dose of drug or vehicle control at least six animals are used.

Compared to vehicle control, it is expected that the intraperitoneal injection of the NMDA receptor antagonists 30 minutes prior to formalin injection into the hindpaw will significantly inhibit formalin-induced pain in a dose-dependent manner as determined by the reduction of the time spent

licking by the mouse of the formalin injected hindpaw caused by increasing doses of NMDA receptor antagonist.

It is known that cortical spreading depression (CSD) can be blocked by competitive and noncompetitive NMDA antagonists, suggesting that NMDA receptor mechanisms mediate the initiation and/or propagation of CSD (Marannes *et al.*, *Brain Res 457*:226-240 (1988)). Glutamate receptor blockade also exerts an effect on anoxic depolarization and CSD (Lauritzen *et al.*, *J. Cereb. Blood Flow Metab. 12*:223-229 (1992)). Thus, NMDA-mediated neurotransmission appears to be essential for the propagation of CSD and represents an important mechanism in migraine headaches.

CSD is elicited by intracortical microinjection of 1M KCl (150 nl) in anesthetized rats and the propagation rate is determined by monitoring the hyperemic response associated with CSD along the ipsilateral parietal cortex. The electroencephalogram (EEG) is also monitored continually in each experiment. In control experiments, CSD elicits a consistent transient (10 min) reduction in total EEG power and the CSD propagation rate does not change significantly over a 4 hour observation period when CSD is evoked at 30 min intervals. NMDA receptor antagonists cause dose-related inhibition of the EEG suppression and cortical hyperemia associated with CSD, and reduce the CSD propagation rate. High affinity NMDA receptor antagonists have a delayed onset of action (inversely related to dose) and a prolonged duration of action at all doses (2 h). In contrast, low affinity NMDA receptor antagonists have a rapid onset of action (30 min) and a predictable dose-related duration of action (PCT Application WO95/06468, published March 9, 1995).

The effects of a particular NMDA receptor antagonist on migraine headaches caused by CSD may be evaluated as follows. Changes in the propagation rate, EEG power and cortical perfusion (CP) are determined in anesthetized rats. Male Sprague-Dawley rats weighing 350-375 g are housed in a thermally controlled (25°C), 12-hour light-cycled (light onset at 0600h) laboratory animal facility with free access to food and water until the day of

experimentation. All drugs are prepared in saline and administered by the intravenous route in volumes not exceeding 0.3 ml. The general surgical procedure has been described previously (Willette *et al.*, *Stroke 21*:451-458 (1990)). Briefly, surgical anesthesia is induced with 2.5% isoflurane in 100% O_2. The left femoral artery is cannulated with polyethylene tubing for the continuous measurement of arterial blood pressure and periodic sampling of arterial blood gasses. The femoral vein is prepared similarly for the intravenous administration of drugs. A tracheostomy is performed and the isoflurane anesthesia is discontinued. Anesthesia is then maintained by slowly administering pentobarbital (40 mg/kg, i.v.) over the next 10 minutes. This procedure provides stable anesthesia for at least 1 hour. Lidocaine ointment (5%) is applied to the femoral and cervical incisions prior to closing with wound clips. Anesthesia and a stable blood pressure and heart rate are maintained for approximately 3-4 hours by administering supplemental doses of pentobarbital (10 mg/kg, i.v.) at 30 min intervals.

Each rat is placed prone in a stereotaxic instrument (DKI, Tujunga, California) and is secured in a flat skull position. A small thermostatic heating pad is placed beneath the abdomen to maintain rectal temperature at 37-38°C. The right frontal and parietal bones are exposed and rostral, intermediate and caudal burr holes (2 mm dia.) are prepared with the dura intact. Each rat is then paralyzed with tubocurarine (1 mg/kg, i.v.) and ventilated artificially with a rodent aspirator (Harvard Apparatus, South Natick, Massachusetts) at a rate of 75 breaths per min and a volume of 3-4 ml/breath. Automated blood gas analysis is performed periodically and ventilation parameters are adjusted to maintain arterial $PaCO_2$, PaO_2 and pH within the ranges of 33.5-38 mm Hg, 75 mm Hg and 7.35-7.45, respectively. Micromanipulators are used to place Laser-Doppler Flowmetry (LDF) needle probes (LF21, Transonic Systems, Inc. Itaca, NY) 4 mm apart in the immediate and rostral cranial windows and local cortical perfusion (CP) is monitored continuously. The stainless steel housing of each probe is used for recording the EEG. EEG power is determined between 1 and 16 Hz as

described previously (Willette *et al.*, *Stroke* *23*:703-711 (1992)). A third micromanipulator is used to position a glass micropipette (40 µm O.D>) 0.5 mm beneath the cortical surface in the caudal cranial window. Following a 20-30 minute acclimation period, CSD is elicited by microinjecting 1M KCl (150 nl) at the caudal site. Vehicle or drugs are administered intravenously after the electrical and cerebrovascular effects of the initial CSD have subsided (8-10 min after KCl microinjection). The microinjection of KCl is then repeated every 30 min for at least 2 hours and the changes in CP, EEG power and propagation rate associated with CSD are determined.

Multiple comparisons with control values are evaluated with ANOVA for repeated measures followed by post hoc analysis with the Bonferroni two-tailed *t* test (Wallenstein *et al.*, *Circ. Res.* *47*:1-9 (1980)). The dose needed to cause a 50% reduction in the CSD propagation rate (ED_{50}) is determined graphically. All summary values are expressed as mean ± SEM, and differences are considered significant at $p \leq 0.05$.

The cortical microinjection (150 nl) of KCl (1M) elicits CSD in the rat. CSD is associated with a slight reduction in CP followed rapidly by a large transient hyperemia and a delayed prolonged (approximately 30 min) oligemia (approximately 20 reduction in CP). A reduction in the EEG power, particularly at the higher frequencies (>4 Hz), accompanies the hyperemic response. With the exception of the oligemic phase, which is observed only after the initial CSD, the responses associated with CSD are highly reproducible when elicited with KCl at 30 min intervals for up to 4 hrs. No significant effects on arterial blood pressure or heart rate are observed.

The delay in the onset of the hyperemic response between the caudal and rostral LDF probe is used to calculate the rate of CSD propagation. The basal propagation rate was 3.7±0.12 mm/min. In vehicle (saline) treated animals, the rate of CSD propagation does not change significantly when evoked repeatedly over 4 hrs. Compared to vehicle control, it is expected that the intravenous administration of the NMDA receptor antagonists will

significantly inhibit KCl-induced EEG suppression and cortical hyperemia associated with CSD, and reduce the CSD propagation rate.

Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, e.g. humans, orally at a dose of 0.0025 to 50 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated for anxiety disorders, e.g., generalized anxiety disorder, phobic disorders, obsessional compulsive disorder, panic disorder, migraine headache and post traumatic stress disorders. Preferably, about 0.01 to about 10 mg/kg is orally administered to treat or prevent such disorders. For intramuscular injection, the dose is generally about one-half of the oral dose. For example, for treatment or prevention of anxiety, a suitable intramuscular dose would be about 0.0025 to about 15 mg/kg, and most preferably, from about 0.01 to about 10 mg/kg.

In the method of treatment or prevention of neuronal loss in ischemia, brain and spinal cord trauma, hypoxia, hypoglycemia, and surgery, as well as for the treatment of Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Down's Syndrome, or in a method of treating a disease in which the pathophysiology of the disorder involves hyperactivity of the excitatory amino acids or NMDA receptor-ion channel related neurotoxicity, the pharmaceutical compositions of the invention may comprise the compounds of the present invention at a unit dose level of about 0.01 to about 50 mg/kg of body weight, or an equivalent amount of the pharmaceutically acceptable salt thereof, on a regimen of 1-4 times per day. When used to treat chronic pain or to induce anesthesia, the compounds of the invention may be administered at a unit dosage level of from about 0.01 to about 50mg/kg of body weight, or an equivalent amount of the

pharmaceutically acceptable salt thereof, on a regimen of 1-4 times per day. Of course, it is understood that the exact treatment level will depend upon the case history of the animal, e.g., human being, that is treated. The precise treatment level can be determined by one of ordinary skill in the art without undue experimentation.

The unit oral dose may comprise from about 0.01 to about 50 mg, preferably about 0.1 to about 10 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets each containing from about 0.1 to about 10, conveniently about 0.25 to 50 mg of the compound or its solvates.

In the method of treating glaucoma, in particular the reduction or prevention of damage to retinal ganglion cells and their axons comprising the optic nerve, the pharmaceutical compositions of the invention may comprise the compounds of the present invention at a unit dose level of about 0.01-50 mg/kg of body weight, on a regimen of 1-4 times per day. The compounds are preferably administered topically, orally or intravitreally. While individual needs vary, determination of optimal ranges of effective amounts is within the skill of the art.

In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those preparations which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragees, and capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 0.01 to 99 percent, preferably from about 0.25 to 75 percent of active compound(s), together with the excipient.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the particular NMDA subunit selective antagonist or agonist of the present invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, and the like. Basic salts are formed by mixing a solution of the particular haloperidol analog of the present invention with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

The pharmaceutical compositions of the invention may be administered to any animal which may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetyl-cellulose phthalate or hydroxypropymethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The characterization of NMDA subunit binding sites *in vitro* has been difficult because of the lack of selective drug ligands. Thus, the NMDA ligands of the present invention may be used to characterize the NMDA subunits and their distribution. Particularly preferred NMDA subunit selective antagonists and agonists of the present invention which may be used for this purpose are isotopically radiolabelled derivatives, e.g. where one or more of the atoms are replaced with ^{3}H, ^{11}C, ^{14}C, ^{15}N, or ^{18}F.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

Examples

Example 1 Binding Assays at NMDA receptor subunits

Preparation of RNA. cDNA clones encoding the NR1A, NR2A, NR2B, NR2C and NR2D rat NMDA receptor subunits were provided by Dr. P. H. Seeburg (*see*, Moriyoshi *et al.*, *Nature (Lond.) 354*:31-37 (1991); Kutsuwada *et al.*, *Nature (Lond.) 358*:36-41 (1992); Monyer *et al.*, *Science (Washington, D.C.) 256*:1217-1221 (1992); Ikeda *et al.*, *FEBS Lett. 313*:34-38 (1992); Ishii *et al.*, *J. Biol. Chem. 268*:2836-2843 (1993) for details of these clones or their mouse homologs). The clones were transformed into appropriate host bacteria and plasmid preparations were made with conventional DNA purification techniques. A sample of each clone was linearized by restriction enzyme digestion and cRNA was synthesized with T3 RNA polymerase. The cRNA was diluted to 400 ng/μl and stored in 1 μl aliquots at -80°C until injection.

The Xenopus oocyte expression system. Mature female *Xenopus laevis* were anaesthetized (20-40 min) using 0.15% 3-aminobenzoic acid ethyl ester (MS-222) and 2-4 ovarian lobes were surgically removed. Oocytes at developmental stages IV-VI (Dumont, J.N., *J. Morphol. 136*:153-180 (1972)), were dissected from the ovary still surrounded by enveloping ovarian tissues. Follicle-enclosed oocytes were micro-injected with 1:1 mixtures of cRNA:NR1A + NR2A, 2B, 2C or 2D; injecting ~2, 5, or 20 ng of RNA encoding each receptor subunit. NR1A encoding cRNA was injected alone at ~20 ng. Oocytes were stored in Barth's medium containing (in mM): NaCl, 88; KCl, 1; $CaCl_2$, 0.41; $Ca(NO_3)_2$, 0.33; $MgSO_4$, 0.82; $NaHCO_3$, 2.4; HEPES 5; pH 7.4, with 0.1 mg/ml gentamycin sulphate. While oocytes were still surrounded by enveloping ovarian tissues the Barth's medium was supplemented with 0.1% bovine serum. Oocytes were defolliculated 1-2 days following injections by treatment with collagenase (0.5 mg/ml Sigma Type I for 0.5-1 hr) (Miledi and Woodward, *J. Physiol.*

(Lond.) 416:601-621 (1989)) and subsequently stored in serum-free medium.

Electrical recordings were made using a conventional two-electrode voltage clamp (Dagan TEV-200) over periods ranging between 3-14 days following injection. Oocytes were placed in a 0.1 ml recording chamber continuously perfused (5-15 ml min^{-1}) with frog Ringer's solution containing (in mM): NaCl, 115; KCl, 2; $CaCl_2$, 1.8; HEPES, 5; pH 7.4. Drugs were applied by bath perfusion. When using the more rapid flow rates, half-times for mid-chamber solution changes were between 2-3 sec, however, exchange rates for drug solutions at the oocyte surface (i.e. beneath the vitelline envelope and among the tangles of microvilli) were probably considerably longer (Woodward *et al.*, *Mol. Pharmacol. 41*:89-103 (1992)). Zero-Ca^{2+}/Ba^{2+} Ringer had the composition (in mM): NaCl, 115; KCl, 2; $BaCl_2$, 1.8; HEPES, 5; pH 7.4. Intraoocyte injections were made by pneumatic pressure-pulse ejection from micropipettes (Miledi and Parker, *J. Physiol. (Lond.) 357*:173-183 (1984)). Injection solutions of EGTA (40-400 mM) and BAPTA (50-500 mM) were made up in H_2O, pH adjusted to 7.4 with KOH or HCl, and filtered to minimize plugging (Acrodisc-13, 0.2 µM). Pressure was set between 200-400 kPa. The volume of injections was regulated by adjusting the time of pulses (0.1-1 sec) and was estimated by measuring the diameters of ejected droplets.

Data Analysis. The logistic equation (equation 1) was fit to the data for individual concentration-response relations by adjusting the slope factor, n, and the parameter pEC_{50}; pEC_{50} = -log EC_{50} where EC_{50} is the agonist concentration that produces half the maximum response (De Lean *et al.*, *Am. J. Physiol. 235*:E97-E102 (1978)) (Origin: Microcal Software).

$$I/I_{max} = 1/(1 + (10^{-pEC50}/[agonist])^{n}) \qquad \text{Eq. 1}$$

Concentration-inhibition curves were fit with equation 2.

$$I/I_{control} = 1/(1+([antagonist]/10^{-pIC_{50}})^{n}) \qquad \text{Eq. 2}$$

in which $I_{control}$ is the current evoked by agonists alone, $pIC_{50} = -\log IC_{50}$, IC_{50} is the concentration of antagonist that produces half maximal inhibition, and n is the slope factor. For incomplete curves analysis by fitting was unreliable and IC_{50} values were calculated by simple regression over linear portions of the curves (Origin: Microcal Software).

Drugs. Haloperidol (**1**); trifluperidol (**7**); ifenprodil (**8**); **2**, 4-(4-chlorophenyl)-4-hydroxypiperidine (haloperidol metabolite I/R1515); **3**, 3-(4-fluorobenzoyl)propionic acid (haloperidol metabolite III/R11302); **5**, (±)-4-[4-(4-chlorophenyl)-4-hydroxypiperidinyl]-1-(fluorophenyl)-1-butanol (haloperidol metabolite II/reduced haloperidol); **6**, 4-[4-(chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-chlorophenyl)-1-butanone (haloperidol chlorinated analog/R1854) were from Research Biochemicals Inc. (Natick, MA). **12**, 4-benzylpiperidine and **4**, 4-chloro-4'-fluorobutyrophenone were from Aldrich. All other drugs were from Sigma. **9**, **10**, and **11** were synthesized in-house (*see*, the Examples below).

Drugs were initially dissolved at concentrations of 10-100 mM in DMSO. Dilutions were then made to generate a series of DMSO stock solutions over the range 10 μM to 100 mM. Working solutions were made by 1000-3000 fold dilution of stocks into Ringer. At these dilutions DMSO alone had no measurable effects on membrane current responses. Ifenprodil stock solutions were in H_2O. DMSO stock solutions of haloperidol and related compounds, and H_2O stock solutions of ifenprodil, were stored for up to two weeks in the dark at 4°C without apparent reductions in potency. Ringer solutions of drugs were made up fresh each day of use.

Results

Fig. 1 depicts sample records illustrating inhibition of NMDA receptor currents by haloperidol in an oocyte expressing the NR1A/2B. The holding potential was -70 mV. Response amplitudes for pharmacological assays were measured under steady-state conditions during the second, or plateau, phase of the response. Inward current is denoted by downward deflection. Drugs were applied as indicated by bars and dead-time of the perfusion system was approximately 5 s. To minimize rundown of responses exposures to agonists were separated by 5-10 min intervals of wash.

Fig. 2 depicts concentration-inhibition curves comparing the sensitivities of four subunit combinations of cloned NMDA receptors to haloperidol; experiments were carried out as described for Fig. 1. In this and all following graphs data points are the mean ± S.D. with currents expressed as a fraction of control responses: NR1A/2A, currents elicited by 10 μM glycine and 100 μM glutamate; NR1A/2B-D, currents elicited by 1 μM glycine and 100 μM glutamate.

Figs. 3A and 3B depict the effects of haloperidol on concentration-response curves for glycine and glutamate at NR1A/2B subunit combinations. Fig. 3A depicts A glycine concentration-response curve; glutamate fixed at 100 μM. The EC_{50} for glycine under control conditions was 0.25 ± 0.01 μM (mean ± S.D.). Haloperidol (5 μM) reduced maximum responses by 61 ± 6% and this inhibition was associated with a reduction in EC_{50} to 0.19 ± 0.02 μM. Fig. 3B depicts A glutamate concentration-response curve; glycine fixed at 10 μM. Under control conditions, the EC_{50} for glutamate was 1.6 ± 0.2 μM. Haloperidol reduced maximum responses by 55 ± 2%, and inhibition was associated with a reduction in EC_{50} to 1.0 ± 0.02 μM. All currents were normalized by expression as a fraction of maximum responses under control conditions prior to applications of haloperidol.

Fig. 4 depicts the haloperidol inhibition of NR1A/2B responses measured at different holding potentials. Oocytes were exposed to a saturating concentration of agonists (10 μM glycine and 100 μM glutamate).

Inhibition induced by 3 μM haloperidol was measured on the established response. The experiments were repeated assaying levels of inhibition at different holding potentials (n = 4; * only one measurement). Levels of inhibition (expressed as a fraction of the control response) appeared to show no dependence upon voltage over the range -110 to +10 mV. *Inset*, sample records. Drug application bars: upper - agonists, lower - haloperidol. Scale bars: 100 nA (-100 and -70 mV), 50 nA (-40 mV), 20 nA (+10 mV), 2 min (all records). To preclude activation of endogenous Cl^- currents oocytes were injected with ~200 pmoles BAPTA and recordings were made in Ba^{2+}-Ringer.

Fig. 5 depicts the kinetics of inhibition at NR1A/2B. On a pre-established response, inhibition by 30 μM haloperidol shows a relatively rapid onset to a steady-state level, while wash follows a more complex timecourse consisting of fast and slow components. Simultaneous application of agonists with 30 μM haloperidol results in a brief spike of current, suggesting brief activation of channels which are then rapidly blocked by haloperidol. Pretreating the oocyte with haloperidol abolishes the spike of current indicating that the inhibitor is able to interact with the receptor prior to channel activation; i.e. that it does not appear to behave like an open-channel channel blocker. To preclude activation of endogenous Cl^- currents oocytes were injected with ~200 pmoles BAPTA and recordings were made in Ba^{2+}-Ringer.

Fig. 6 depicts the concentration-inhibition curves comparing potencies of haloperidol, haloperidol metabolites and related compounds at NR1A/2B subunit combinations.

Fig. 7 depicts concentration-inhibition curves for 2 at four putative NMDA receptor subtypes.

Fig. 8 depicts concentration-inhibition curves for trifluperidol at four NMDA receptor subtypes.

Fig. 9 depicts concentration-inhibition curves for ifenprodil at four NMDA receptor subtypes.

Fig. 10 concentration-effect curves for 13 at four NMDA receptor subtypes. Note that 13 causes potentiation of currents in oocytes expressing NR1A/2A receptors. Also note the limited efficacy inhibition of currents in oocytes expressing NR1A/2B receptors. NR1A/2C and 2D combinations were largely unaffected.

Example 2 The Potency Profiles of Haloperidol Analogs

The structure-activity relationship for the subunit-selective action of haloperidol was examined by testing compounds which are structurally related. These compounds were either commercially available (e.g. Research Biochemicals Inc.), or were synthesized (see below). The results are shown in Table 1.

Table 1. Summary of results. IC_{50} values were determined by curve fitting to logistic equations (see Examples). Data is expressed as the mean ± S.D. with the number of experiments in parentheses (each using a separate oocyte), otherwise n = 1 or 2.

Antagonist	IC_{50} (μm)			
	NR1A/NR2A	NR1A/NR2B	NR1A/NR2C	NR1A/NR2D
1	>100 (6)	2.7±0.7 (5)	>100 (5)	>100 (3)
2	209±43 (3)	71±13 (4)	337±23 (3)	600±100 (3)
3	>300 (2)	>300 (4)	>300 (5)	NT[a]
4	>300	50	>300	200
5	84±43 (3)	65±12 (3)	176±23 (5)	>100
6	>100 (2)	125±3 (3)	123±7 (3)	>100
7	69±4 (3)	1.7±0.3 (3)	>100 (2)	>100 (3)
8	7.5±3.8 (3)	0.2±0.03 (3)	63±7 (3)	>100 (3)
9	100	4	>100	>100 (4)
10	100	6	>100	>100 (2)

Antagonist	IC_{50} (μm)			
	NR1A/NR2A	NR1A/NR2B	NR1A/NR2C	NR1A/NR2D
11	>100	>100	>100	>100
12	30	15	>100	>100
13	Potentiation 44±14% (3) (max)	Inhibition 7.3±3.9 (2)	Potentiation 5.7±2.1% (3) (max)	Inactive
18	40	>100	>100	>100
16	30	6	>100	>100
20	>100	>100	>100	>100
22	>100	>100	>100	>100
24	>100	>100	NT	NT
25a	NT	>100	>100	NT
26	90	0.5	>100	NT
27	>300	>100	>100	NT
28	>300	12	>300	NT
29	170	1.5	250	NT

[a]NT = Not tested

Example 3 Preparation of 4-(4-Benzylpiperidinyl)-4'-fluorobutyrophenone (9).

A solution of 1.01 g (5.76 mmol) of 4-benzylpiperidine (12) and 0.595 g (2.96 mmol) of 4-chloro-4'-fluorobutyrophenone (4) and 16 mg of NaI in 10 mL of toluene was refluxed for 28 h. It was cooled to room temperature, diluted by 10 mL of hexane, filtered and washed by hexane. The filtrate was evaporated to leave 1.01 g of oil which was purified by chromatography (silica gel, hexane:ethyl acetate = 20:1, 10:1, 5:1, 10:3, 5:2, 200 mL each) to give 672 mg (81%) of solid, mp 58-59°C. ^{1}H NMR ($CDCl_3$), 1.23 (m, 2), 1.50 (m, 1), 1.604 (sb, 2), 1.850 (t, 2), 1.914 (m, 2), 2.352 (t, 1), 2.498 (d, 2), 2.856 (d, 2), 2.943 (t, 2) 7.12 (m, 5), 7.25 (m, 2),

7.989 (m, 2). MS, 339 (M^+, 15), 201 (100), 188 (100), 123 (80). HRMS, Calcd for $C_{22}H_{26}FNO$ 339.1991, Found 339.1999.

Example 4 Preparation of 3-(4-Benzylpiperidinyl)-4'-fluoropropiophenone (10).

A solution of 1.07 g (6.10 mmol) of 4-benzylpiperidine (12) and 0.567 g (0.304 mmol) of 3-chloro-4'-fluoropropiophenone (14) and 14 mg of NaI in 10 mL of toluene was refluxed for 24 h. It was cooled to room temperature, diluted by 10 mL of hexane, filtered and washed by hexane. The filtrate was evaporated to leave 1.09 g of oil. Portion (199 mg) of the oil was purified by preparative TLC (20x20 cm, hexane:ethanol = 8:1, Rf = 0.3-0.4) to give 140 mg of oil. It was dissolved in 3 mL of ethanol and to the solution kept in ice-bath was added dropwise 0.1 mL of concentrated HCl (37%) to produce crystalline solid. It was filtered and washed by 0.5 mL of methanol, dried to give 134 mg (61%) of white solid, mp 198-199°C. ^1H NMR ($CDCl_3$), 1.805 (m, 3), 2.062 (m, 2), 2.632 (m, 4), 3.405 (q, 2), 3.525 (d, 2), 3.815 (t, 2), 7.111-7.315 (m, 7), 8.039 (m, 2), 12.39 (mb, 1). MS, 325 (M^+, 20), 188 (100), 175 (50), 125 (90). HRMS, Calcd for $C_{21}H_{24}FNO$ 325.1835, Found 325.1851.

Example 5 Preparation of 3-[4-(4-Chlorophenyl)-4-hydroxypiperidinyl]-4'-fluoropropiophenone (11).

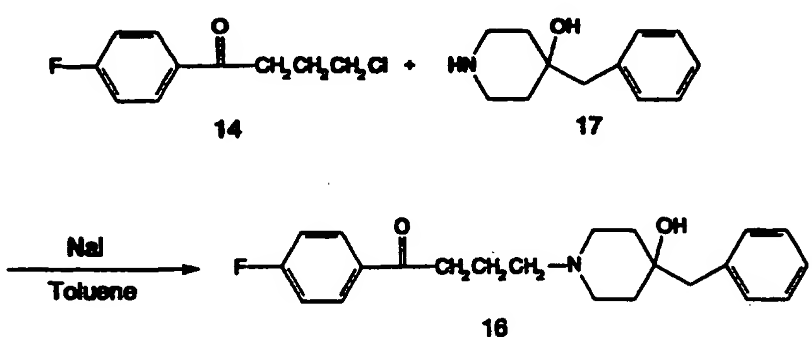
A mixture of 312 mg (1.47 mmol) of 4-(4-chlorophenyl)-4-hydroxypiperidine (2) and 140 mg (0.750 mmol) of 3-chloro-4'-fluoropropiophenone (14) and 15 mg of NaI in 5 mL of toluene was refluxed for 4 h. It was cooled to room temperature, filtered and washed by $CHCl_3$ (15 mL). The filtrate was evaporated to leave 250 mg of white solid which was stirred with 15 mL of ether, filtered and dried to give 210 mg (77%) of white solid, mp 158-159°C. ^1H NMR ($CDCl_3$), 1.753 (d, 2), 2.145 (m, 2), 2.582 (t, 2), 2.870 (d, 2), 2.935 (t, 2), 3.230 (t, 2), 7.114 (t, 2), 7.318 (d, 2),

7.442 (d, 2). 8.009 (dd, 2), MS, 361 (M^+, 5), 224 (15), 211 (20), 193 (40), 123 (100). HRMS, Calcd for $C_{20}H_{21}ClFNO_2$ 361.1238, Found 361.1239.

Example 6 Preparation of 4-[4-(4-Chlorophenyl)-4-hydroxypiperidinyl]-butyrophenone (13).

A mixture of 213 mg (1.00 mmol) of 4-(4-chlorophenyl)-4-hydroxypiperidine (2) and 97 mg (0.53 mmol) of 4-chlorobutyrophenone (15) and 20 mg of NaI in 5 mL of toluene was refluxed for 24 h. It was cooled to room temperature, filtered and washed by ether (10 mL). The filtrate was evaporated to leave yellow oil which was dissolved in ether (3 mL). The solution was added into 10 mL of hexane and allowed to stand for 0.5 h. The crystalline solid was filtered and washed by ether:ethyl acetate = 2:1 (1 ml) and hexane (2 mL), dried to leave pale yellow solid 55 mg (29%), mp 125-126°C (lit. 129-130°C; Janssen *et al.*, *J. Med. Pharm. Chem.* *1*:281 (1959)). ^{1}H NMR ($CDCl_3$), 1.660 (d, 2), 2.010 (m, 4), 2.517-2.422 (m, 4), 3.798 (m, 2), 3.014 (t, 2), 7.292 (d, 2), 7.371 (d, 2), 7.469 (t, 2), 7.565 (t, 1), 7.995 (d, 2).

Example 7 Preparation of 4-(4-Benzyl-4-hydroxypiperidinyl)-4'-fluorobutyrophenone (16).

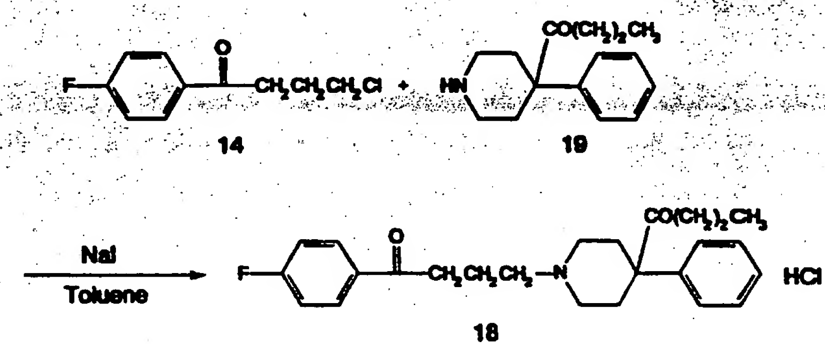


14 17

16

A solution of 382 mg (1.99 mmol) of 4-benzyl-4-hydroxypiperidine (17) and 199 mg (0.991 mmol) of 4-chloro-4'-fluorobutyrophenone (14) and 46 mg of NaI in 10 mL of toluene was refluxed for 36 h. It was cooled to room temperature and filtered and the oily solid was washed by hexane. The combined solution was evaporated to leave oily solid which was washed by hexane (2 x 10 mL), dried to leave 120 mg (34%) of oily solid. ^{1}H NMR ($CDCl_3$), 1.50 (m, 2), 1.70 (m, 2), 1.958 (m, 2), 2.333 (t, 2), 2.462 (t, 2), 2.731 (m, 4), 2.967 (t, 2), 7.120-7.313 (m, 7), 7.99 (m, 2). MS, 355 (M^+, 10), 264 (12), 217 (100). HRMS, Calcd for $C_{22}H_{26}FNO_2$ 355.1940, Found 355.1943.

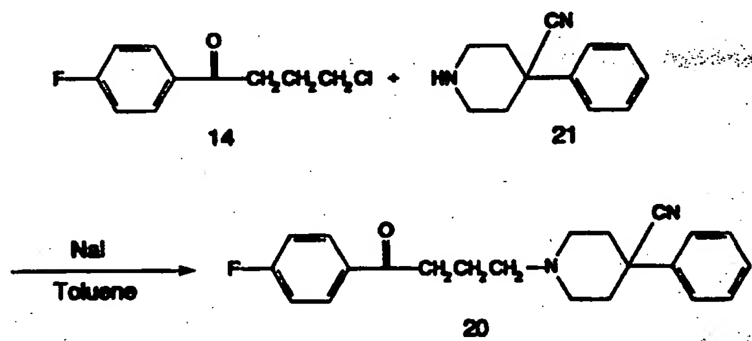
Example 8 Preparation of 4-(4-Butyryl-4-phenylpiperidinyl)-4'-fluorobutyrophenone (18).



A solution of 538 mg (2.00 mmol) of 4-butyryl-4-phenylpiperidine hydrochloride (19), 194 mg (0.966 mmol) of 4-chloro-4'-fluorobutyrophenone (14), 204 mg (2.01 mmol) of Et_3N and 86 mg of NaI in 10 mL of toluene was refluxed for 36 h. It was cooled to room temperature, filtered and washed by hexane. The filtrate was evaporated and the residue was treated by hexane, filtered and washed by hexane, dried to leave pale-yellow solid. A portion of the solid was purified by preparative TLC and developed by ethylacetate : hexane : methanol = 1 : 1 : 0.1 to give 38 mg (10%) of oily solid. ^{1}H NMR ($CDCl_3$), 0.659 (t, 3), 1.415 (m, 2), 1.945 (m, 2), 2.01 (m, 2), 2.157 (t, 2), 2.399 (m, 4), 2.69 (m, 2), 2.961 (t, 2),

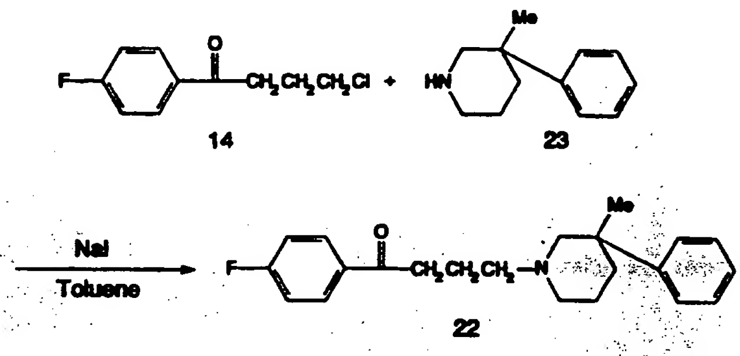
3.117 (t, 2), 3.756 (t, 2), 7.14 (m, 2), 7.24-7.33 (m, 5), 8.00 (m, 2). MS, 395 (M^+, 10), 324 (15), 244 (100). HRMS, Calcd for $C_{25}H_{30}FNO_2$ 395.2252, Found 395.2278.

Example 9 Preparation of 4-(4-Cyano-4-phenylpiperidinyl)-4'-fluorobutyrophenone (20).



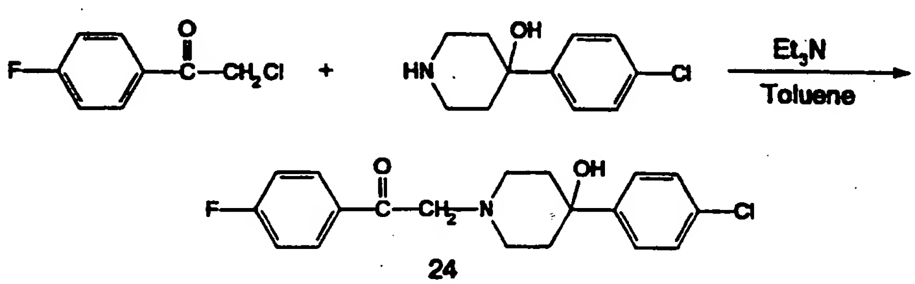
A solution of 146 mg (0.655 mmol) of 4-cyano-4-phenylpiperidine hydrochloride (21), 155 mg (0.772 mmol) of 4-chloro-4'-fluorobutyrophenone (14), 143 mg (1.41 mmol) of Et_3N and 10 mg of NaI in 5 mL of toluene and 5 mL of $CHCl_3$ was refluxed for 2 days. It was cooled to room temperature, filtered and washed by hexane. The filtrate was evaporated to leave an oily solid. It was purified by preparative TLC and developed by ethyl acetate : hexane = 1 : 1 to give 99 mg of solid. The solid was stirred with 5 mL of hexane and 1 mL of ether for 2 h, filtered and washed by hexane, dried to leave 52 mg (23%) of white solid, mp 60-61°C. ^1H NMR ($CDCl_3$), 2.012 (m, 6), 2.522 (m, 4), 2.979 (m, 4), 7.138 (t, 2), 7.316-7.442 (m, 5), 8.015 (m, 2). MS, 350 (M^+, 5), 212 (100). HRMS, Calcd for $C_{22}H_{23}FN_2O$ 350.1787, Found 350.1824.

Example 10 ***Preparation of 4-(3-Methyl-3-phenylpiperidinyl)-4'-fluorobutyrophenone (22).***



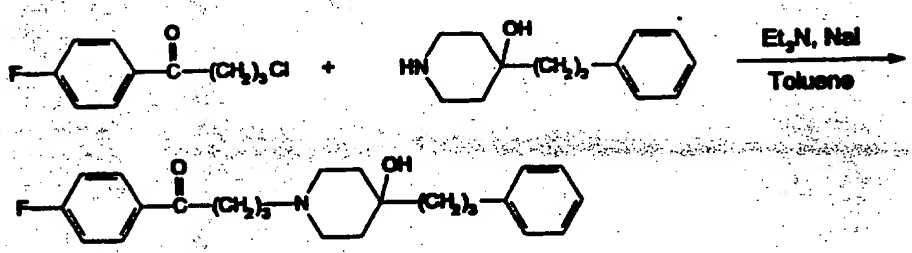
A solution of 359 mg (2.05 mmol) of 3-methyl-3-phenylpiperidine (23), 201 mg (1.00 mmol) of 4-chloro-4'-fluorobutyrophenone (14) and 30 mg of NaI in 5 mL of toluene was refluxed for 24 h. It was cooled to room temperature, filtered and washed by hexane. The filtrate was evaporated to leave an oil. It was purified by preparative TLC developed by ethyl acetate : hexane = 1 : 6 to give 182 mg (53%) of oil. ^{1}H NMR ($CDCl_3$), 1.234 (s, 3), 1,587 (m, 4), 1.947 (m, 3), 2.392 (m, 4), 2.75 (m, 1), 2.993 (t, 2), 7.139 (m, 3), 7.260 (t, 2), 7.384 (d, 2), 7.976 (m, 2). MS, 339 (M^+, 5), 201 (70), 188 (100). HRMS, Calcd for $C_{22}H_{26}FNO$ 339.1991, Found 339.1989.

Example 11 ***Preparation of 2-[4-(4-chlorophenyl)-4-hydroxypiperidinyl]-4'-fluoroacetophenone (24).***



A mixture of 2-chloro-4'-fluoroacetophenone (86 mg, 0.50 mmol), 4-(4-chlorophenyl)-4-hydroxypiperidine (106 mg, 0.5 mmol), Et_3N (250 mg, 2.47 mmol) in toluene (5 mL) was refluxed for 3 h, cooled to rt, filtered and washed with hexane (2 x 5 mL). The filtrate was evaporated, and the residue was chromatographed over silica gel (EtOAc-EtOH, 98 : 2) to give 41 mg (23%) of **24** as a brown-yellow powder, mp 150-2°C. ^{1}H NMR ($CDCl_3$): 1.73-2.10 (m, 3H), 2.20-2.30 (m, 2H), 2.63-2.71 (m, 2H), 2,91-2.95 (m, 2H), 3.880 (s, 2H), 7.141 (t, 2H, J=8.6), 7.319 (d, 2H, J=8.5), 7.442 (d, 2H, J=8.5), 8.062 (dd, 2H, J=8.5; 6). Purity was 98.6% by HPLC.

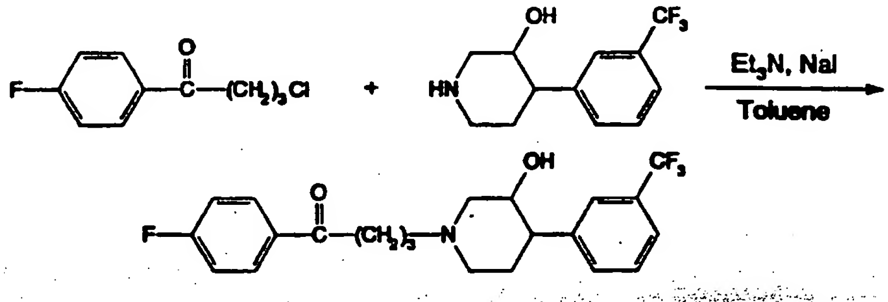
Example 12 Preparation of 4-[4-Hydroxy-4-(3-phenylpropyl)piperidinyl]-4'-fluorobutyrophenone (25a).



25a

A mixture of 4-hydroxy-4-(3-phenylpropyl)piperidine (200 mg, 0.91 mmol, obtained from the hydrochloride), 4-chloro-4'-fluorobutyrophenone (200 mg, 1.0 mmol), Et_3N (40 mg, 4.0 mmol), NaI (50 mg, 0.33 mmol) and toluene (10 mL) was refluxed for 18 h, cooled to rt, filtered and washed with hexane (2 x 10 mL). The filtrate was evaporated, and the residue was chromatographed over silica gel (EtOAc) to give 150 mg (40%) of **25a** as a yellow viscous oil. ^{1}H NMR ($CDCl_3$): 1.41-1.59 (m, 5H), 1.64-1.72 (m, 4H), 1.90-1.99 (m, 2H), 2.22-2.31 (m, 2H), 2.401 (t, 2H, J=7), 2.58-2.63 (m, 4H), 2.945 (t, 2H, J=7), 7.095 (t, 2H, J=8.6), 7.16-7.30(m, 5H), 7.98 (dd, 2H, J=8.5; 6). HRMS, Calcd for $C_{24}H_{30}FNO_2$: 383.2253; Found: 383.2257. Purity was 99.7% by HPLC. The hydrochloride **25b**, mp 150-1°C.

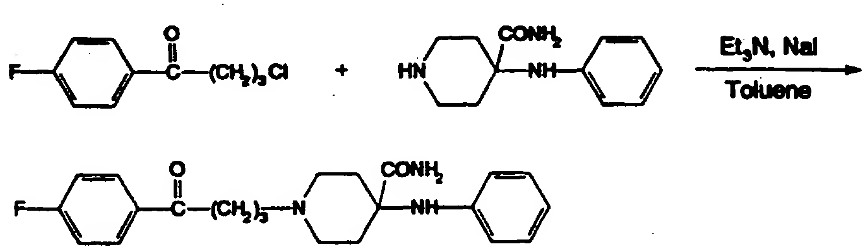
Example 13 Preparation of 4-[3-hydroxy-4-(3-trifluoromethylphenyl)piperidinyl]-4'-fluorobutyrophenone (26).



26

A mixture of 4-(3-trifluoromethyl)phenyl-3-piperidinol (240 mg, 1.0 mmol, obtained from the hydrochloride), 4-chloro-4'-fluorobutyrophenone (204 mg, 1.0 mmol), Et_3N (40 mg, 4.0 mmol), NaI (50 mg, 0.33 mmol) and toluene (10 mL) was refluxed for 18 h, cooled to rt, filtered and washed with hexane (2 x 5 mL). The filtrate was evaporated, and the residue was chromatographed over silica gel (EtOH-EtOAc, 10 : 0.5) to give 70 mg (30%) of 26 as a yellow powder, mp 85-6°C. ^{1}H NMR ($CDCl_3$): 1.66-1.70 (m, 3H), 1.95-2.05 (m, 4H), 2.39-2.51 (m, 4H), 2.79-2.82 (m 2H), 2.983 (t, 2H, J=7), 7.139 (t, 2H, J=8.5), 7.42-7.64 (m, 3H), 7.726 (s, 1H), 8.022 (dd, 2H, J=8.5; 6). HRMS, Calcd for $C_{22}H_{23}F_4NO_2$: 409.1658; Found: 409.1667. Purity was 98.7% by HPLC.

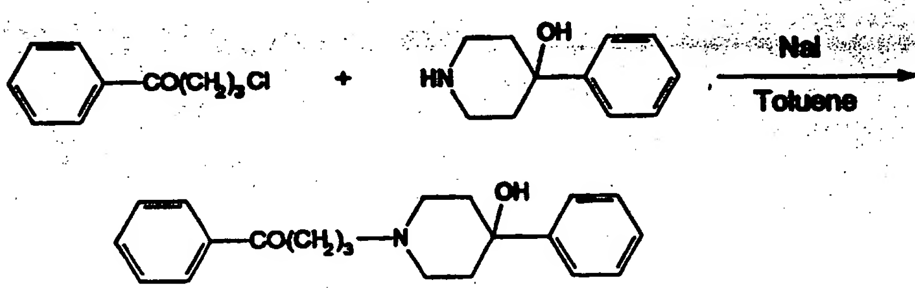
Example 14 Preparation of 4-(4-Anilino-4-carbamylpiperidinyl)-4'-fluorobutyrophenone (27).



27

A mixture of 4-chloro-4'-fluorobutyrophenone (240 mg, 1.2 mmol), 4-anilino-4-carbamylpiperidine (220 mg, 1.0 mmol), Et_3N (556 mg, 5.5 mmol), NaI (55 mg) and toluene (15 mL) was refluxed for 16 h, cooled to rt, filtered and washed with hexane (3 x 5 mL). The filtrate was evaporated, and the residue was chromatographed over silica gel (EtOAc-EtOH, 8 : 2) to give 80 mg (21%) of 27 as a brown-yellow powder, mp 163-4°C. ^1H NMR ($CDCl_3$): 1.87-1.94 (m, 4H), 2.04-2.12 (m, 2H), 2.21-2.31 (m, 2H), 2.401 (t, 2H, J=7), 2.74-2.78 (m, 2H), 2.986 (t, 2H, J=7), 3.998 (s, 1H), 5.284 (bs, 2H), 6.624 (d, 2H, J=8), 6.78-6.88 (m, 2H), 7.10-7.21 (m, 3H), 8.000 (dd, 2H, J=9; 5.5). HRMS, Calcd for $C_{22}H_{26}FN_3O_2$: 383.2002; Found: 383.2013. Purity was 99.2% by HPLC.

Example 15 ***Preparation of 4-(4-hydroxy-4-phenylpiperidinyl)-butyrophenone (28).***

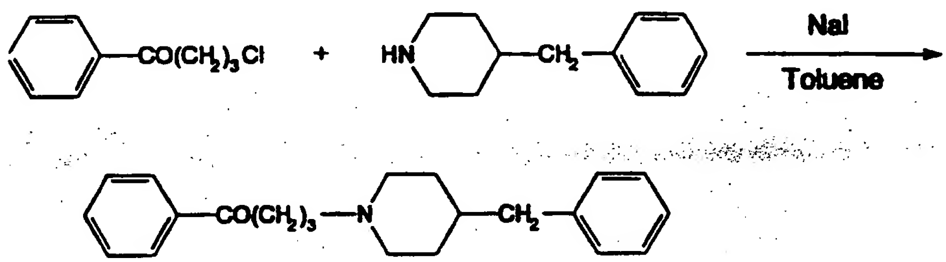


28

A mixture of 4-chlorobutyrophenone (185 mg, 1.0 mmol), 4-hydroxy-4-phenylpiperidine (360 mg, 2.0 mmol), NaI (75 mg) and toluene (15 mL) was refluxed for 24 h, cooled to rt, filtered and washed with hexane (2 x 10 mL). The filtrate was evaporated, and the residue was chromatographed over silica gel (EtOAc-EtOH, 10 : 1) to give 118 mg (36%) of 28 as a yellow powder, mp 113-4°C. ^1H NMR ($CDCl_3$): 1.52 (bs, 1H), 1.68-1.72 (m, 2H), 1.90-2.10 (m, 4H), 2.40-2.52 (m, 4H), 2.78-2.82 (m, 2H), 3.020 (t, 2H, J=7), 4H), 7.344 (t, 2H, J=7.5), 7.45-7.56 (m, 6H), 7.993 (d, 2H, J=7.5).

Analysis, Calcd for $C_{21}H_{25}NO_2$: C 77.99, H 7.79, N 4.33; Found: C 78.08, H 7.81, N 4.26.

Example 16 Preparation of 4-(4-Benzylpiperidinyl)butyrophenone (29a) and the hydrochloride (29b).



29a

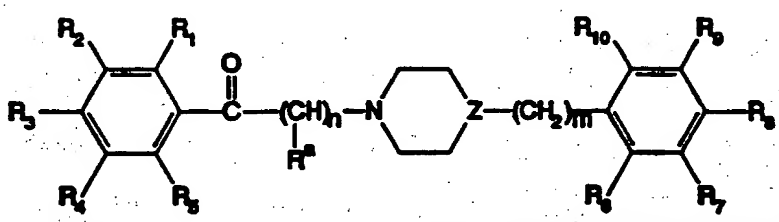
A mixture of 4-chlorobutyrophenone (1.05 g, 6.0 mmol), 4-benzylpiperidine (540 mg, 3.0 mmol), NaI (120 mg) and toluene (15 mL) was refluxed for 3 days and cooled to rt. It was filtered and washed with hexane (3 x 15 mL) and the filtrate was evaporated. The residue was chromatographed over silica gel (EtOAc-EtOH, 10 : 1) to give 524 mg (54%) of **29a** as a yellowish powder, mp 61-2°C. ^{1}H NMR ($CDCl_3$): 1.16-1.29 (m, 2H), 1,44-1.53 (m, 1H), 1.57-1.61 (m, 2H), 1.82-1.98 (m, 4H), 2.367 (t, 2H, J=7), 2.504 (d, 2H, J=7), 2.85-2.89 (m, 2H), 2.982 (t, 2H, J=7), 7.11-7.29 (m, 4H), 7.43-7.58 (m, 4H), 7.70 (d, 2H, J=8). The hydrochloride **29b**, mp 159-60°C. Analysis, Calcd. for $C_{22}H_{28}ClNO$: C 73.83, H 7.88, N 3.91; Found: C 73.55, H 7.81, N 3.81.

***

Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

1. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;

wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

Z is one of N, CH, COH, CCN, CCHO, $CCONH_2$, CCO-alkyl, CCO-alkenyl, CCH_2NHCO-alkyl, CHO-alkyl or CNR^dR^e, wherein R^d and R^e are independently alkyl groups;

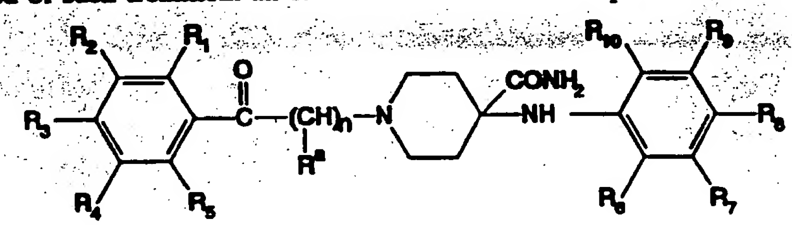
R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy or carboxy;

n is 1 to 5; and

m is 0 to 3.

2. The method of claim 1, wherein said compound is 4-(4-benzyl-4-hydroxypiperidinyl)-4'-fluorobutyrophenone, 4-(4-butyryl-4-phenyl-piperidinyl)-4'-fluorobutyrophenone, 4-(4-hydroxy-4-phenylpiperidinyl)-butyrophenone, 4-(4-benzylpiperidinyl)butyrophenone, 4-(4-benzylpiperidinyl)-4'-fluorobutyrophenone, 3-(4-benzylpiperidinyl)-4'-fluoropropiophenone or 4-[4-(4-chlorophenyl)-4-hydroxypiperidinyl]butyrophenone.

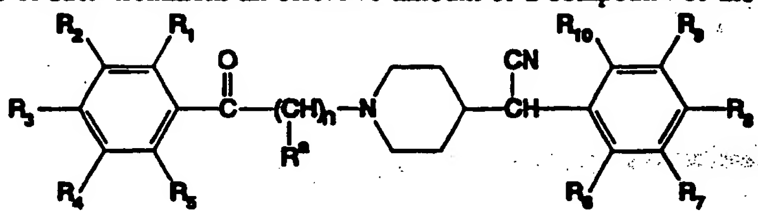
3. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;
wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy or carboxy; and
n is 1 to 5.

4. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a

neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula

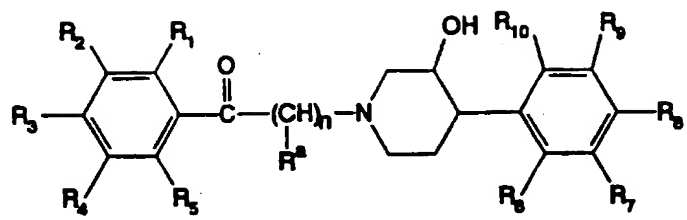


or a pharmaceutically acceptable salt thereof;

wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy or carboxy; and

n is 1 to 5.

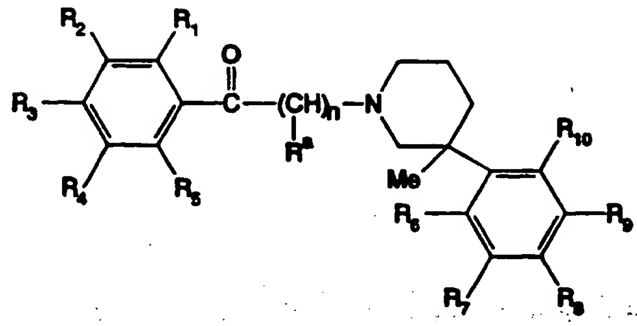
5. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;
wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy or carboxy; and
n is 1 to 5.

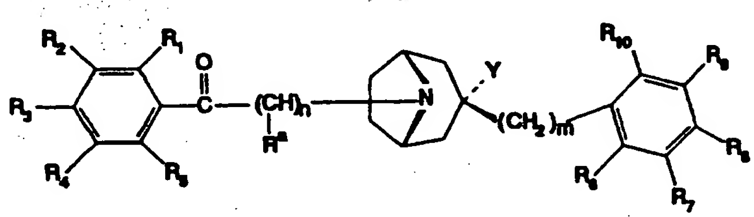
6. The method of claim 5, wherein said compound is 4-[3-hydroxy-4-(3-trifluoromethylphenyl)piperidinyl]-4'-fluorobutyrophenone.

7. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;
wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy or carboxy; and
n is 1 to 5.

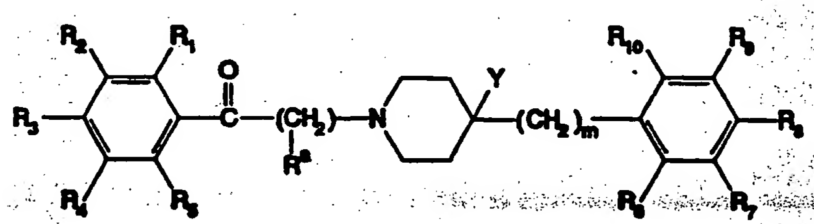
8. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;
wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; n is 1 to 5;
m is 0 to 3;
Y is one of OH, H, CN, CHO, $CONH_2$, CO-alkyl, CO-alkenyl, CH_2NHCO-alkyl, O-alkyl or CO_2-alkyl; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

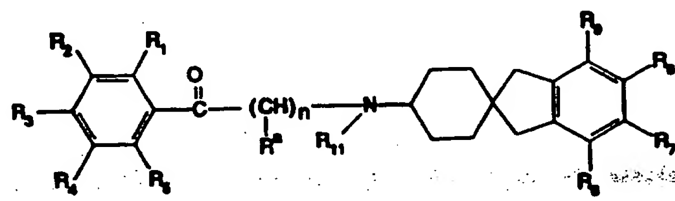
9. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;
wherein R_1-R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; n is 1 to 5;
m is 0 to 3;
Y is OH, H, CN, CHO, $CONH_2$, CO-alkyl, CO-alkenyl, CH_2NHCO-alkyl, O-alkyl and CO_2-alkyl; or
R^a can vary with each repetitive CH group and is independently hydrogen, alkyl, aryl, hydroxy, or carboxy.

10. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences

of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



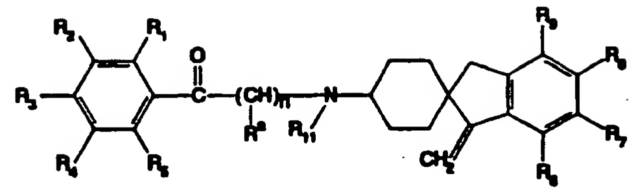
or a pharmaceutically acceptable salt thereof;

R_1 to R_9 are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

11. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



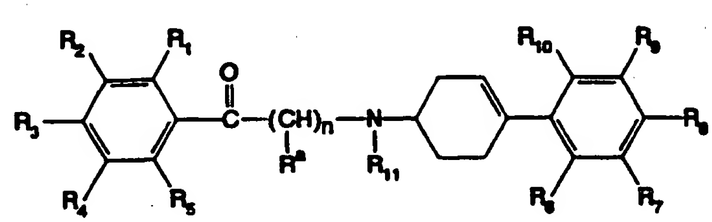
or a pharmaceutically acceptable salt thereof;

R_1 to R_9 are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is one of hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

12. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



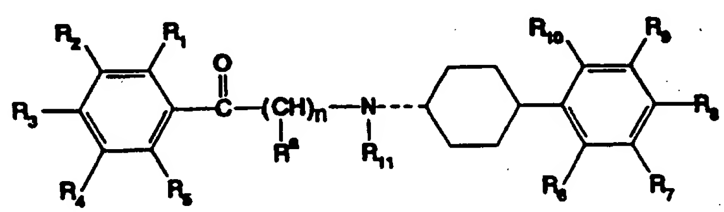
or a pharmaceutically acceptable salt thereof;

R_1 to R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is one of hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

13. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;

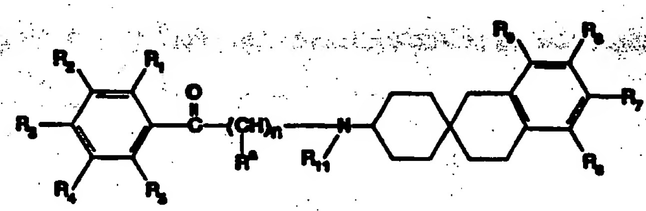
R_1 to R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is hydrogen, aryl, fused aryl, a heterocyclic group, a

heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

14. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



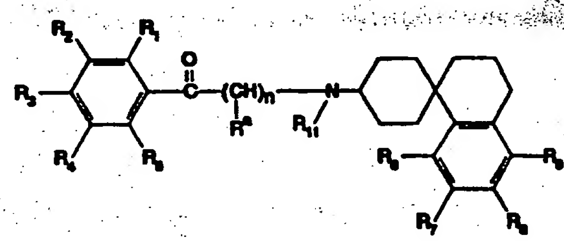
or a pharmaceutically acceptable salt thereof;

R_1 to R_9 are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

15. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;

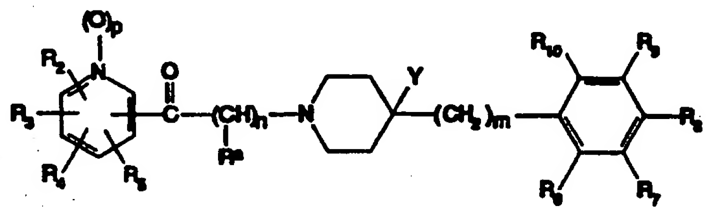
R_1 to R_9 are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; R_{11} is hydrogen, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, or acyl;

n is 1 to 5; and

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

16. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing

anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;

R_2 to R_{10} are each independently one of hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol; m is 0 to 3;

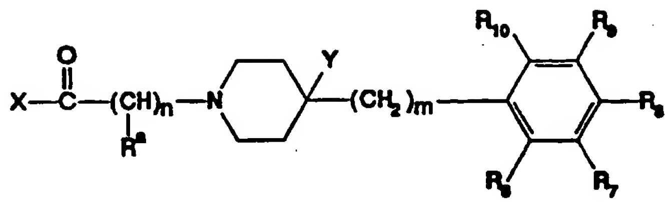
n is 1 to 5;

p is 0 or 1; and

Y is one of OH, H, CN, CHO, $CONH_2$, CO-alkyl, CO-alkenyl, CH_2NHCO-alkyl, O-alkyl or CO_2-alkyl; or

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

17. A method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery, or treating a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula



or a pharmaceutically acceptable salt thereof;

wherein X is an aryl or heteroaryl ring which may be substituted by one or more halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol groups;

m is 0 to 3;

n is 1 to 5;

Y is one of OH, H, CN, CHO, $CONH_2$, CO-alkyl, CO-alkenyl, CH_2NHCO-alkyl, O-alkyl or CO_2-alkyl; or

R^a can vary with each repetitive CH group and is independently one of hydrogen, alkyl, aryl, hydroxy, or carboxy.

18. The method of any one of claims 1-17, wherein said compound is administered as part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

19. The method of any one of claims 1-17, wherein said migraine headache is caused by cortical spreading depression.

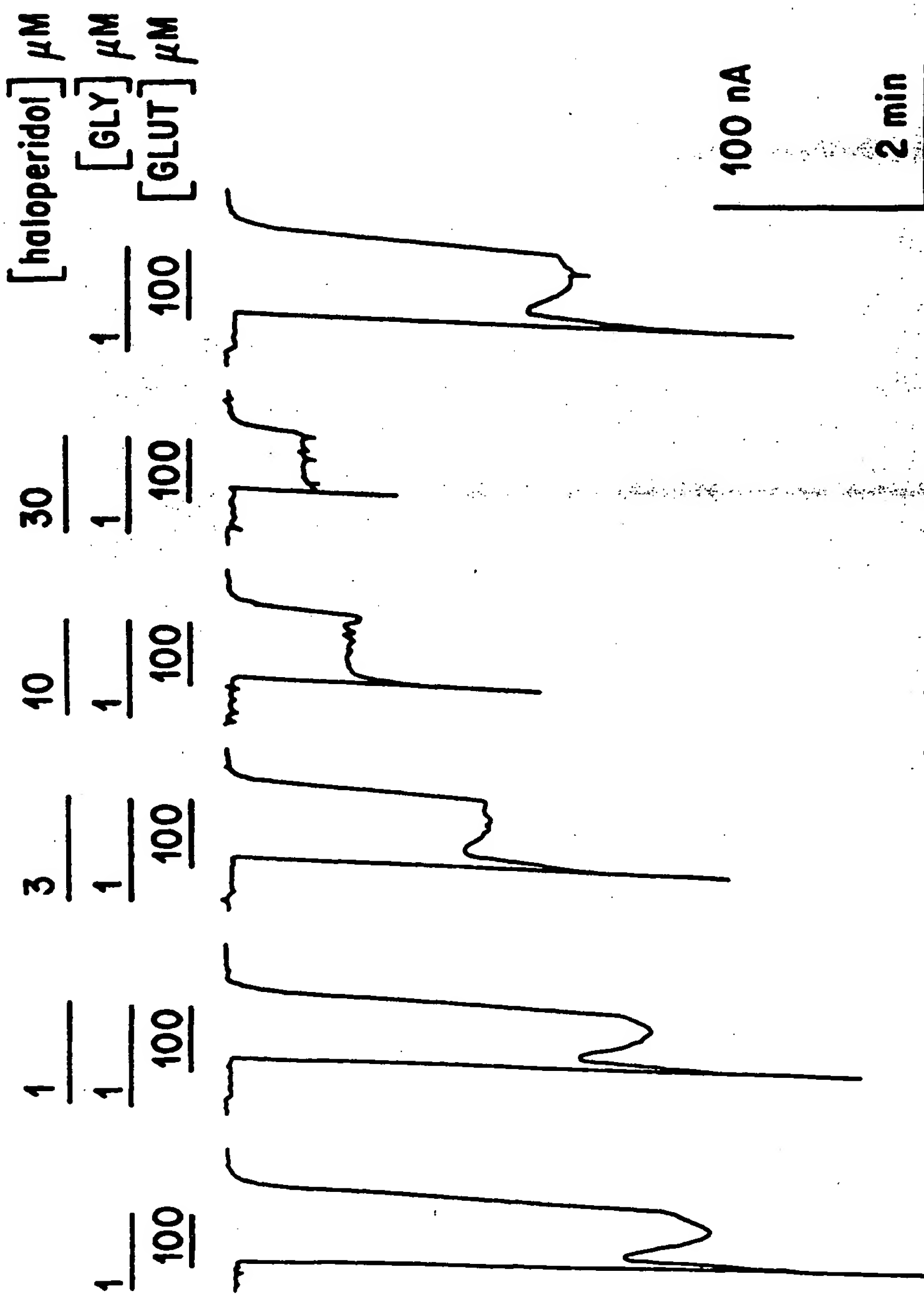
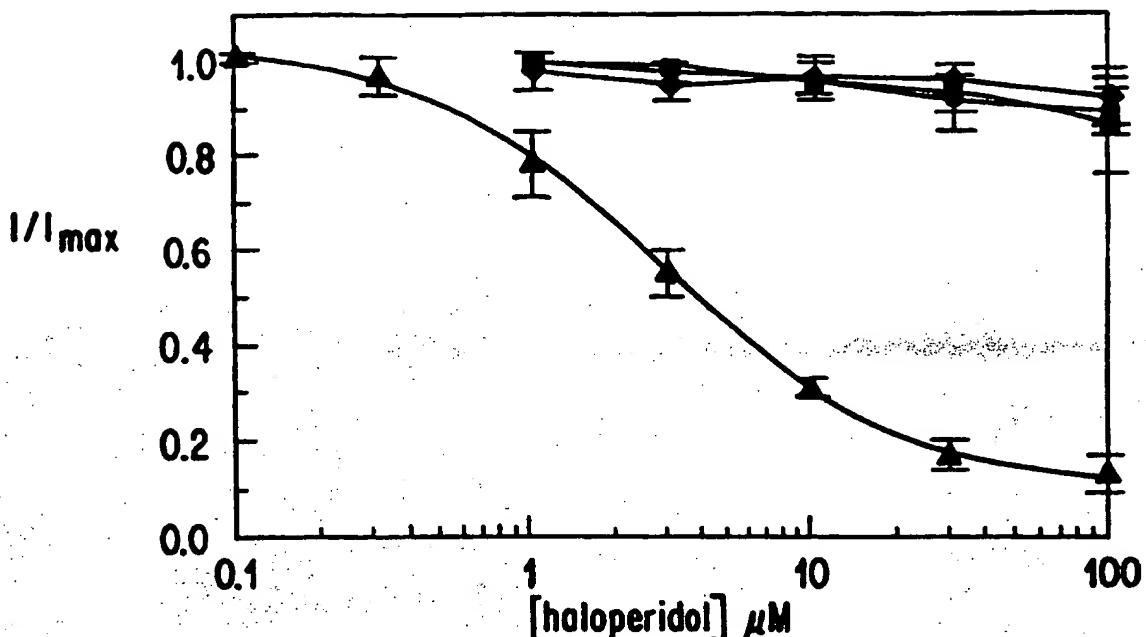
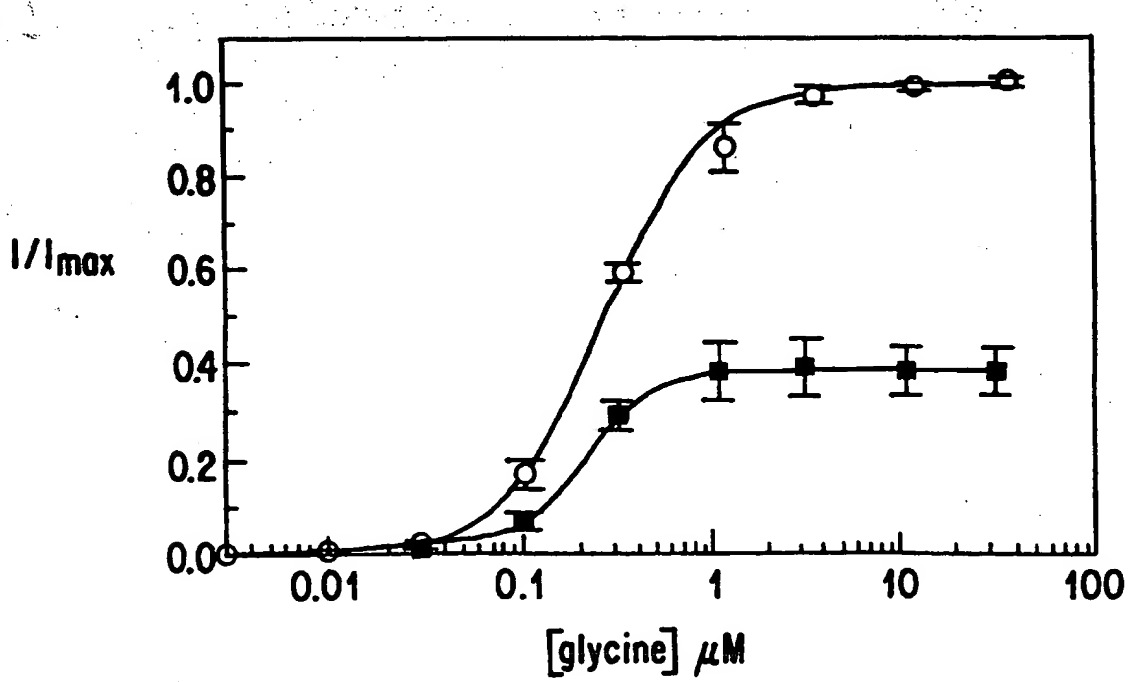

[haloperidol] μM
[GLY] μM
[GLUT] μM
100 nA
2 min
1
100
30
1
100
10
1
100
3
1
100
1
1
100
1
100

FIG. 1



1.0
0.8
0.6
0.4
0.2
0.0
I/Imax
0.1
1
10
100
[haloperidol] μM

FIG. 2



1.0
0.8
0.6
0.4
0.2
0.0
I/Imax
0.01
0.1
1
10
100
[glycine] μM

FIG. 3A

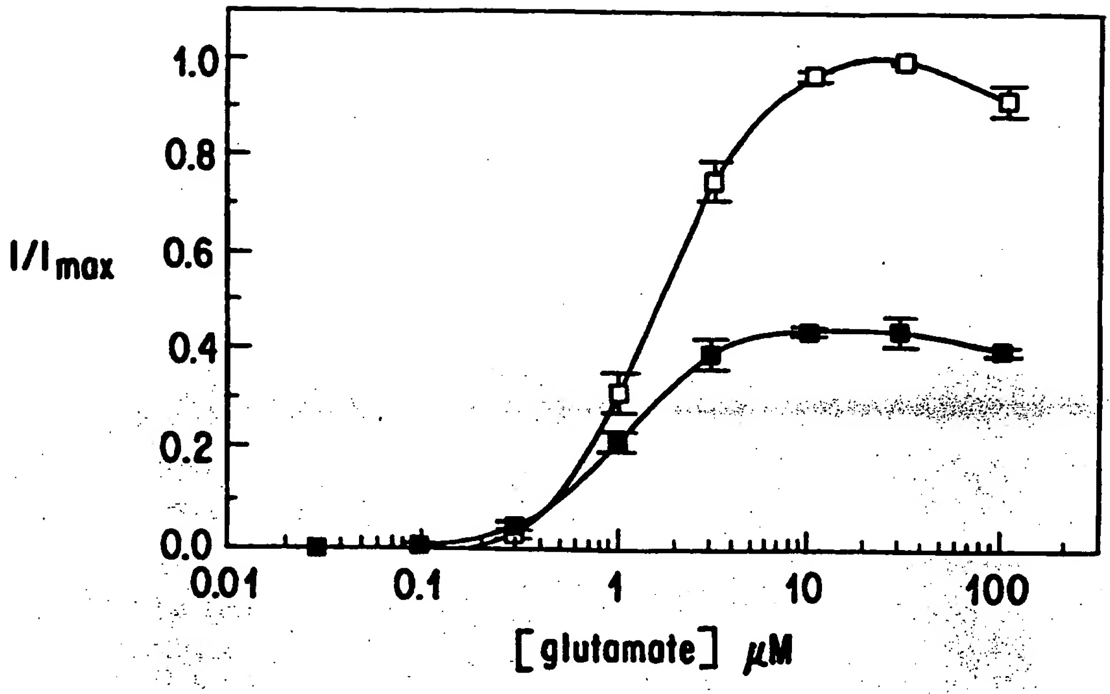

1.0
0.8
I/Imax
0.6
0.4
0.2
0.0
0.01
0.1
1
10
100
[glutamate] μM

FIG. 3B

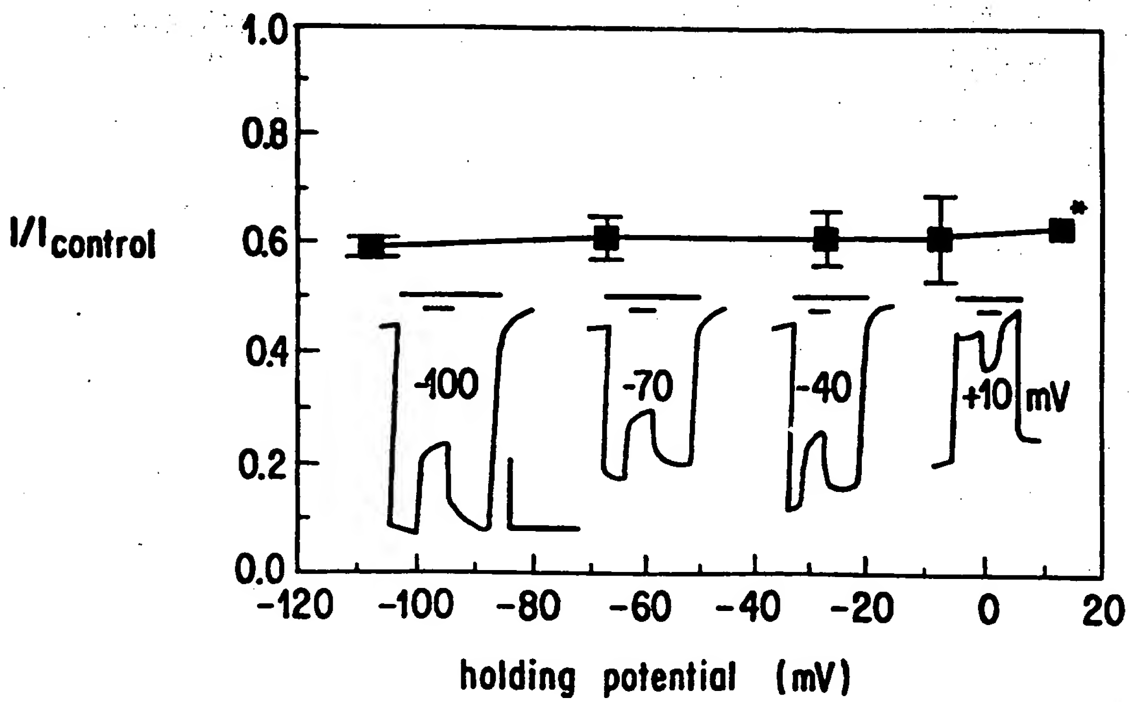

1.0
0.8
I/Icontrol
0.6
0.4
0.2
0.0
-100
-70
-40
+10 mV
-120
-100
-80
-60
-40
-20
0
20
holding potential (mV)

FIG. 4

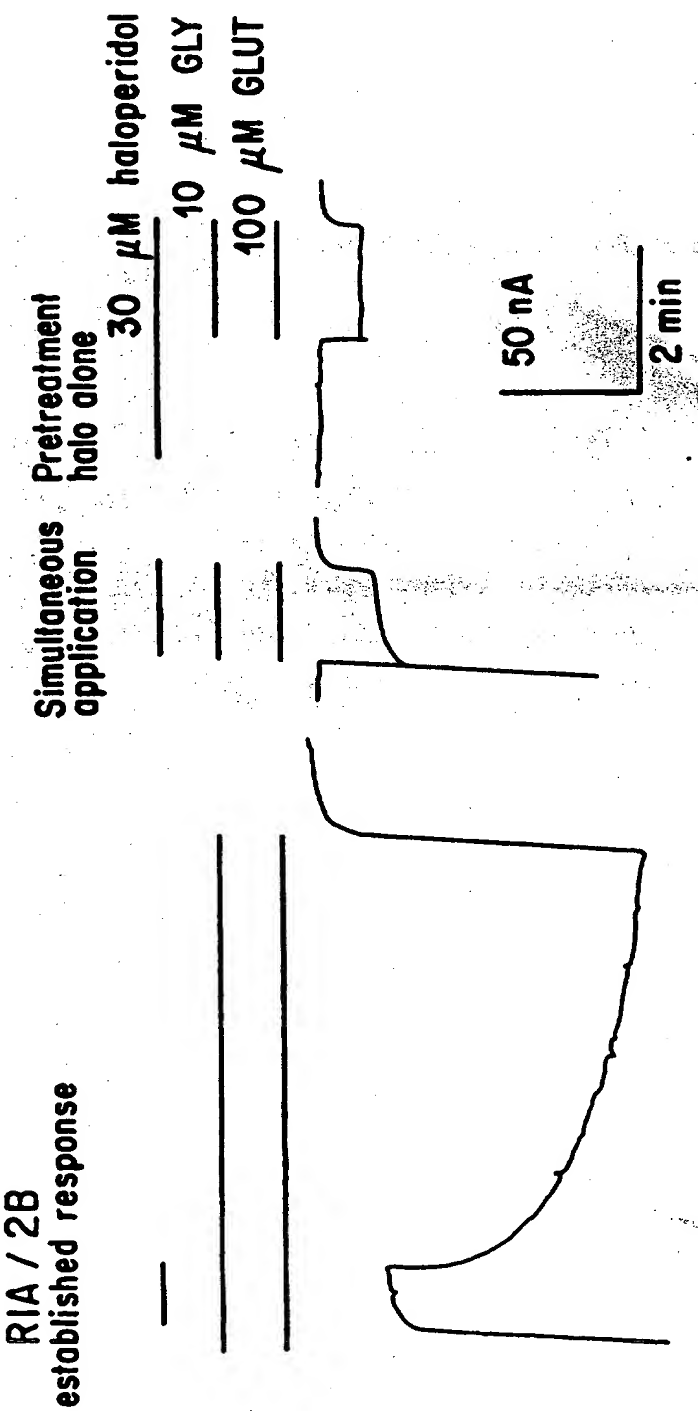
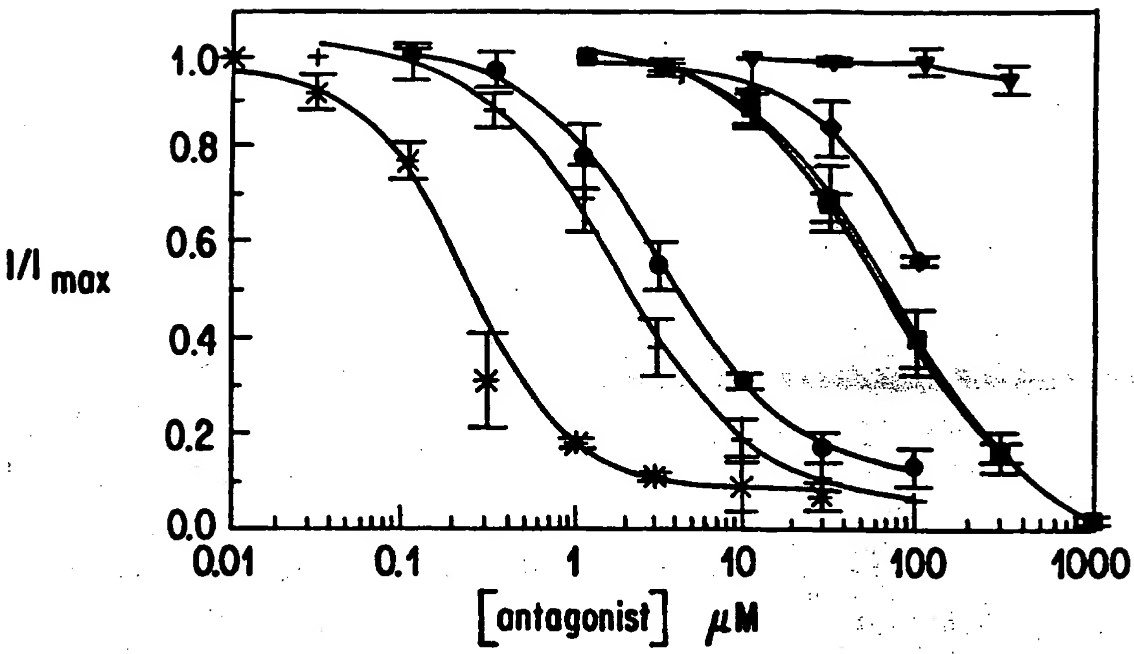
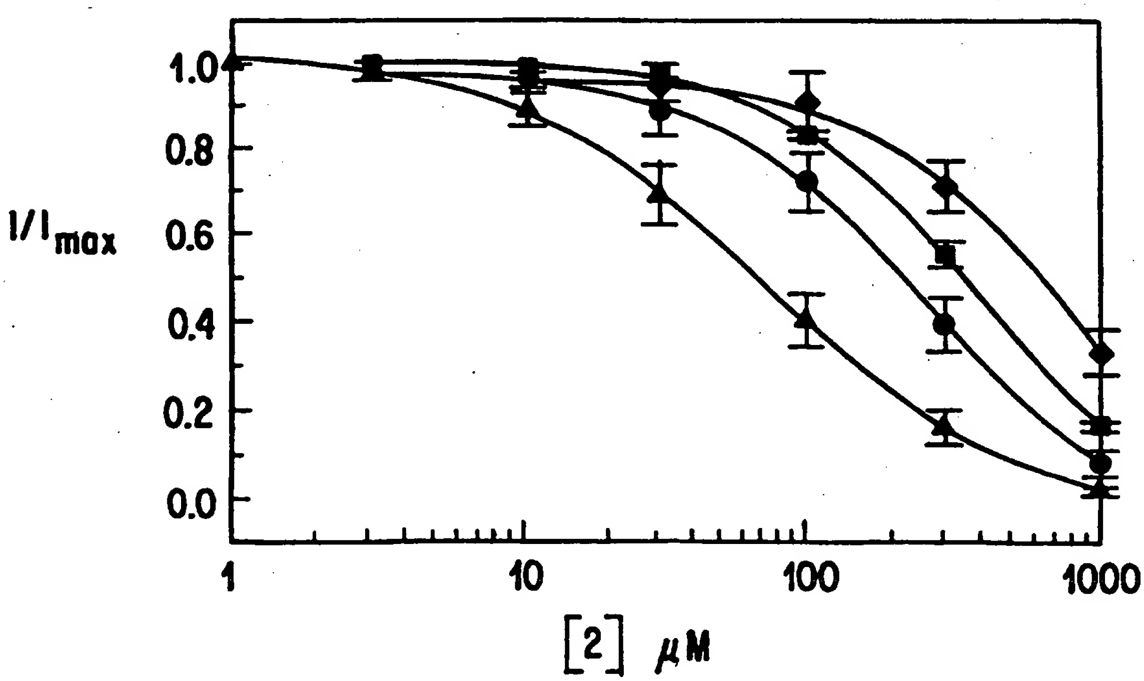

RIA / 2B
established response
Simultaneous
application
Pretreatment
halo alone
30 μM haloperidol
10 μM GLY
100 μM GLUT
50 nA
2 min

FIG. 5



1.0
0.8
0.6
0.4
0.2
0.0
I/I max
0.01
0.1
1
10
100
1000
[antagonist] μM

FIG. 6



1.0
0.8
0.6
0.4
0.2
0.0
I/I max
1
10
100
1000
[2] μM

FIG. 7

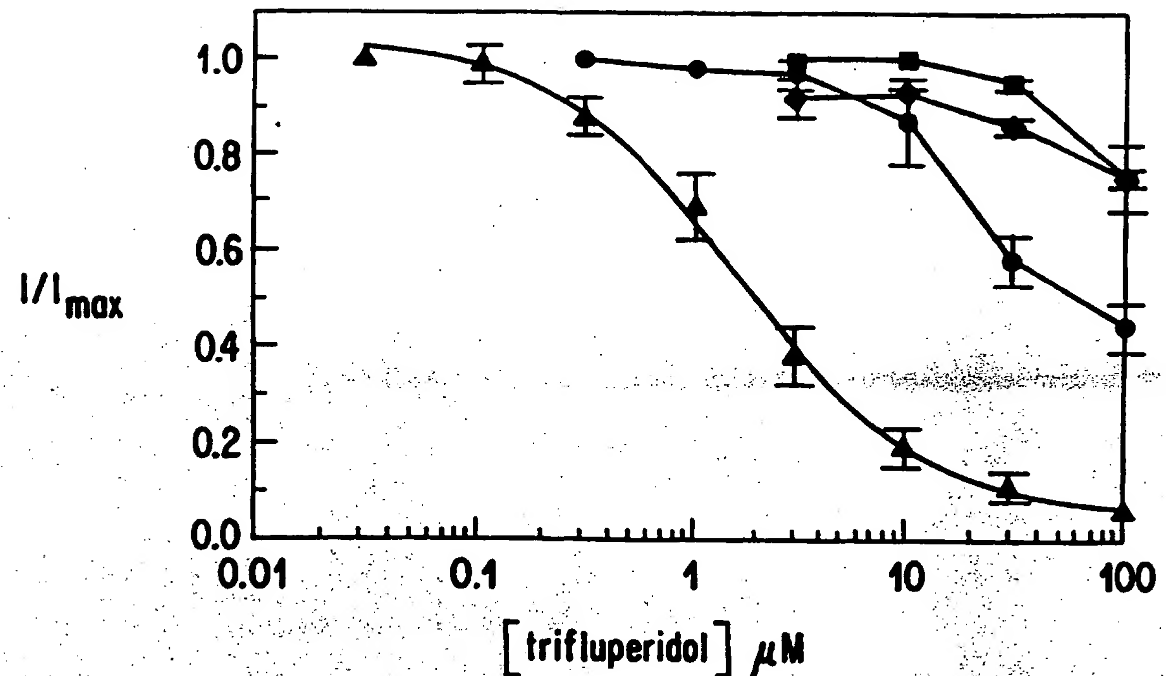

1.0
0.8
0.6
I/Imax
0.4
0.2
0.0
0.01
0.1
1
10
100
[trifluperidol] μM

FIG. 8

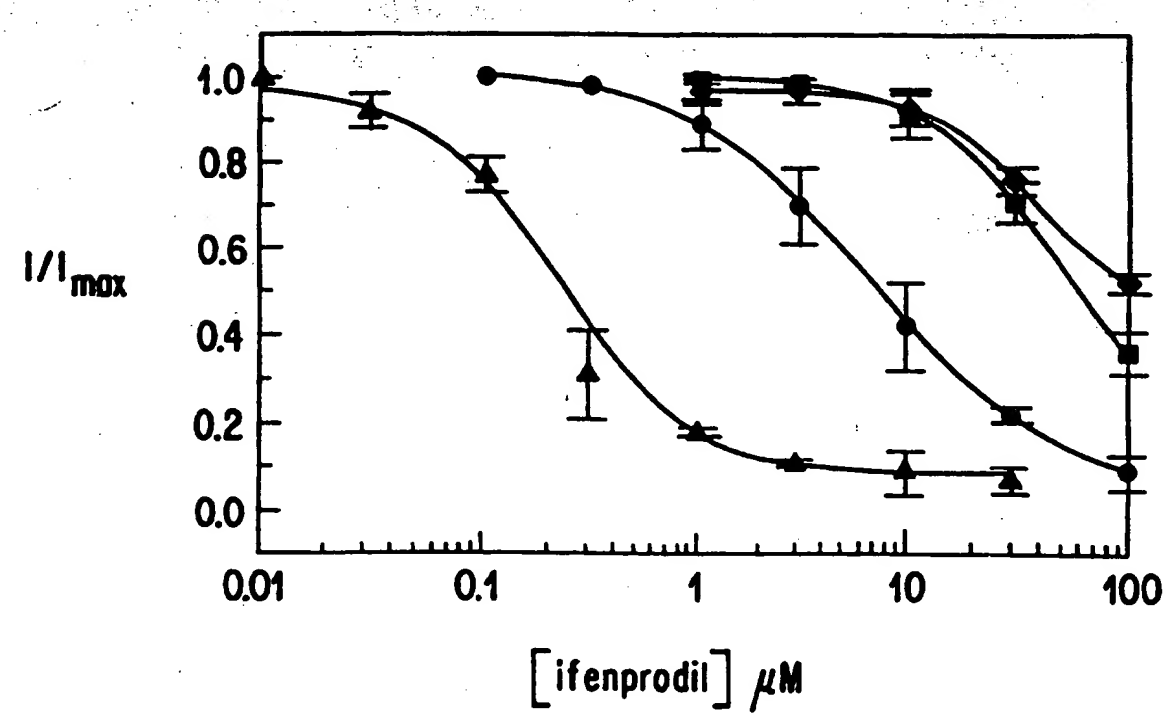

1.0
0.8
0.6
I/Imax
0.4
0.2
0.0
0.01
0.1
1
10
100
[ifenprodil] μM

FIG. 9

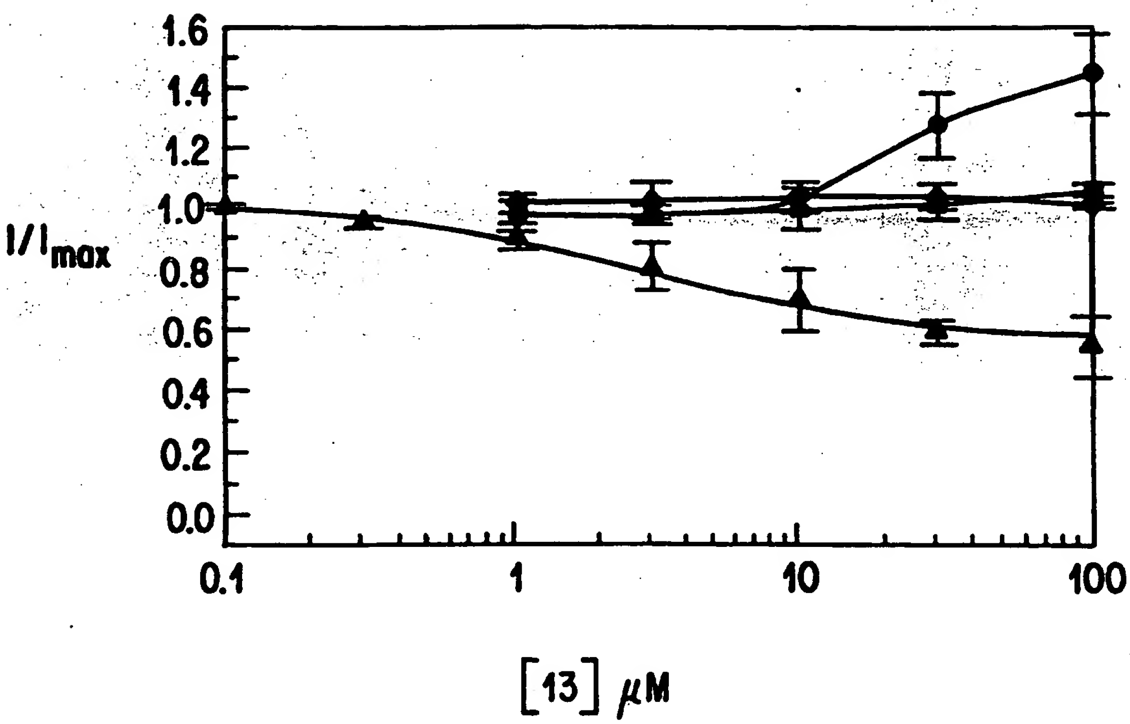


FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/09191

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/445; 31/495
US CL :514/255, 317, 326, 327, 329, 330, 331
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/255, 317, 326, 327, 329, 330, 331

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Neuroscience, Volume 52, Number 4, issued February 1993, MAGAL ET AL. "CONVERGENT REGULATION BY CILIARY NEUROTROPHIC FACTOR AND DOPAMINE OF TYROSINE HYDROXYLASE EXPRESSION IN CULTURES OF RAT SUBSTANTIA NIGRA", pages 867-881, see entire document.	1-7, 9, 17-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 OCTOBER 1995	17 NOV 1995

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Phyllis Spivack aco Lenell Weaver for
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/09191

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-7, 9, 17-19

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I.Claims 1, 18, 19, drawn to a method of treating or preventing neuronal loss, or treating or preventing a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering a compound of claim 1 where Z is nitrogen, in Class 514, subclass 255.

II. Claims 1-7, 9, 17-19, drawn to a method of treating or preventing neuronal loss, or treating or preventing a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering a compound of claim 1 where Z is carbon or the compounds of the Formulas of claims 3, 4, 5, 7, 9, 17 to 19, in Class 514, subclass 315+.

III.Claims 8, 18, 19, drawn to a method of treating or preventing neuronal loss, or treating or preventing a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering a compound of claim 8, in Class 514, subclass 304.IV.Claims 10-15, 18, 19, drawn to a method of treating or preventing neuronal loss, or treating or preventing a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering a compound of claims 10-15, 18, 19, where no heterocycles are present, classified in Class 514, subclass 656.

V.Claims 1-19, drawn to a method of treating or preventing neuronal loss, or treating or preventing a neurodegenerative disease, or treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, or treating anxiety, convulsions, migraine headache, glaucoma, chronic pain or inducing anesthesia, or enhancing cognition, comprising administering a compound of any of claims 1-19 wherein a heterocycle is present, other than those classified in Groups I-III supra, classified in various subclasses of Class 514.

and it considers that the International Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:
Upon thorough consideration of the claims, the Examiner believes that a lack of unity of invention exists, as defined in Rule 13.
PCT Rule 13.1 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention").

PCT Rule 13.2 states that unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features.

In this case, the inventions defined in each Group set forth above are independent and structurally diverse. A reference anticipating one invention would not anticipate or render obvious a claim to another invention. Thus, the inventions are not so linked as to form a single general inventive concept within the meaning of Rule 13.1.